FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

PSYCHOPHARMACOLOGIC DRUGS

ADVISORY COMMITTEE MEETING

NDA 20-639/S-045 and S-046: Seroquel

(quetiapine fumarate) tablets

NDA 20-825/S-032: Geodon

(ziprasidone hydrochloride) capsules

NDA 20-592/S-040 and S-041: Zyprexa

(olanzapine) tablets

JUNE 9, 2009

8:06 a.m.

MARRIOTT CONFERENCE CENTERS

UNIVERSITY OF MARYLAND, UNIVERSITY COLLEGE

UMUC INN AND CONFERENCE CENTER

3501 UNIVERSITY BOULEVARD EAST

ADELPHI, MARYLAND

MEETING ROSTER

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I N D E X

P R O C E E D I N G S

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DR. NGO: Good morning, everyone. We'd like to get started now, please. I would first like to remind everyone present to please silence your cell phones, BlackBerry and other devices if you have not already done so. I would also like to identify our press officer, Ms. Sandy Walsh. Please stand or raise your hand. Thank you.

DR. GOODMAN: Good morning, everybody. I appreciate your willingness to brave the thunderstorms this morning. I'm Wayne Goodman. I'm the acting chair for the Pediatric Drug Advisory Committee hearings both today and tomorrow. First we're going to do a round of introductions. I'll start with myself. I am psychiatrist. I'm also a clinical researcher. Presently run a division in the extramural branch of National Institute of Mental Health here in Maryland.

And to my left, although you can't see her, Dr. Rappley -- I wonder if you could

introduce yourself, say something briefly about your expertise and your affiliation.

DR. RAPPLEY: Yes. Thank you very much. Can you hear me? Hello? Hello? Hello?

DR. GOODMAN: Yes, we can hear you.

DR. RAPPLEY: Okay. I'm from Michigan State University. And my area of expertise is developmental and behavioral pediatrics.

DR. GOODMAN: Let's turn to the other end of the table. Dr. Laughren.

DR. LAUGHREN: Tom Laughren. I'm the director of the division of psychiatry products at FDA.

DR. PRITCHETT: I'm Ed Pritchett. I'm consulting professor of medicine at Duke University Medical Center. I'm a cardiologist and clinical pharmacologist, and my area of interest is anti-arrhythmic drug pharmacology.

DR. GRANGER: I'm Chris Granger. I'm a cardiologist at Duke University, director of the cardiac care unit and clinical trialist.

DR. GREENWAY: I'm Frank Greenway. I'm

an endocrinologist. I direct the outpatient research clinic at the Pennington Center, which is a research campus of Louisiana State University, and my research interest has been in obesity.

DR. TOWBIN: I'm Kenneth Towbin. I'm a child and adolescent psychiatrist in the intermural research program at the National Institute of Mental Health where the focus is on pediatric bipolar disorder and severe mood dysregulation.

MS. LAWRENCE: I'm Margy Lawrence, a patient representative from Potomac, Maryland. I have been involved with NAMI Montgomery County for over ten years as a patient advocate. Thank you.

DR. GRADY-WELIKY: I'm Tana Grady-Weliky. I'm professor of psychiatry at the Oregon Health and Sciences University. I'm a psychiatrist -- general psychiatrist and a psychosomatic psychiatrist.

DR. SCHULTZ: My name is Susan Schultz. I'm professor of psychiatry at the University of Iowa Carver College of Medicine. My specialty is

in geriatric psychiatry, so I'll be looking at things at the later end of the life span.

DR. NGO: My name is Diem-Kieu Ngo, the designated federal official for this meeting.

DR. VITIELLO: Ben Vitiello. I'm a psychiatrist. I'm the chief of the child treatment branch at the National Institute of Mental Health.

DR. GRIFFITH: My name is Gail Griffith. I am the consumer representative to the committee. I am a writer and advocate on behalf of adolescent mental health.

DR. WOOLSON: I'm Robert Woolson. I'm a professor of biostatistics at the Medical University of South Carolina.

DR. CNANN: I'm Avital Cnann. I'm at Children's National Medical Center, and I'm a biostatistician with the focus on pediatric clinical trials.

DR. ROBINSON: Hi. I'm Delbert Robinson. I'm a psychiatrist at the Zucker Hillside Hospital and the Albert Einstein College of Medicine, and I

primarily work in early phase schizophrenia.

DR. GOGTAY: Hi. I'm Nitin Gogtay. I'm a psychiatrist at child psychiatry branch at the NIMH, and my focus is on childhood-onset schizophrenia.

DR. CAPLAN: My name is Rochelle Caplan. I'm a child psychiatrist at UCLA, clinical researcher, primarily in childhood schizophrenia and epilepsy.

DR. DAY: I'm Ruth Day. I'm a cognitive scientist, director of the medical cognition laboratory at Duke University, and do research on how physicians and patients understand, remember and use medical information, especially drugs, with a background in drug safety and risk management.

DR. LESAR: Good morning. Timothy Lesar. I'm the director of clinical pharmacy services at Albany Medical Center in Albany, New York. I also sit on the drug safety and risk management committee, and expertise in drug safety.

DR. TWYMAN: Hi. I'm Roy Twyman. I'm

the industry rep. I'm with Johnson & Johnson. I'm VP for CNS research.

DR. GOODMAN: Okay. Thank you all very much for being here. We should have a very interesting two days. We just started, and I wanted to make a correction about something I said. I got my name right, but I got the name wrong for this meeting. This is PDAC, so let's make sure we're oriented here. That's the Psychopharmacological Drug Advisory Committee, not the Pediatric Advisory Committee, although we do have members from pediatric and our topic really is pediatric.

For topics -- so I'm going to read a prepared statement.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder,

individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion.

A press conference will not be held. This is -- I have an old statement here. A press conference will not be held today, so scratch that.

Although the committee is reminded -- please refrain from discussing the meeting topic during breaks or lunch. Thank you very much. Let me turn it over to Diem for -- our executive secretary for reading of the conflict of interest

statement.

DR. NGO: The Food and Drug Administration is convening today's meeting of the Psychopharmacologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees for other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with the federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC 208 and section 712 of the Federal Food, Drug and Cosmetic Act (FD&C Act) is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 USC section 208, Congress had authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meetings, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts,

grants, CRADAs, teachings, speaking, writing, patents and royalties and primary employment.

The agenda on both days involves discussion of safety and efficacy issues for the following new drug applications: NDA 20-639/S-045 and S-046, Seroquel, quetiapine fumarate, AstraZeneca Pharmaceuticals, LP, for the acute treatment of schizophrenia in adolescents 13 to 17 years of age, and the acute treatment of bipolar mania in children 10 to 12 years of age and adolescents 13 to 17 years of age.

NDA 20-825/S-032, Geodon, ziprasidone hydrochloride, Pfizer, Incorporated, for the acute treatment of manic or mixed episodes associated with bipolar disorder with or without psychotic features in children and adolescents ages 10 to 17 years.

And NDA 20-592/S-040 and S-041, Zyprexa, olanzapine, Eli Lilly and Company, for the acute treatment of manic or mixed episodes associated with bipolar I disorder and the acute treatment of schizophrenia in adolescents ages 13 to 17.

This topic is a particular matter involving specific parties. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 USC section 208 and section 712 of the Food, Drug and Cosmetic Act to Dr. Edward Pritchett for ownership of stock in two competing firms. The magnitude of the interests are between $5,001 to $10,000, and $25,001 to $50,000.

The waivers allow Dr. Pritchett to participate fully in today's deliberations.

FDA's reasons for issuing the waivers are described in the waiver document which is posted on the FDA's website at www.fda.gov/ohrms/dockets/default.htm.

Copies of the waivers may also be obtained by submitting a written request through the agency's Freedom of Information Office, room 630 of the Parklawn Building.

A copy of this statement will be

available for review at the registration table during this meeting and will be included as part of the official transcript.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Roy Twyman is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Twyman's role at this meeting is to represent industry in general and not any particular company. Dr. Twyman is employed by Johnson & Johnson.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firm at

issue. Thank you.

DR. GOODMAN: Okay. Thank you very much, Diem. I notice two additional FDA members joined the table. I wonder if you'd introduce yourselves.

DR. MATHIS: My name is Mitchell Mathis. I'm the deputy director of the division of psychiatry products.

DR. GOODMAN: Bob Temple is also -- he's making a cameo appearance, as you can see.

All right. It's my pleasure to introduce our first speaker, Dr. Tom Laughren of the FDA.

DR. LAUGHREN: Good morning. We appreciate everyone coming out on this stormy morning. This meeting over the next two days is going to focus on safety and efficacy data for three development programs for atypical antipsychotic drugs. These drugs are being proposed for use in treating pediatric patients with schizophrenia and bipolar mania.

The three drugs of interest are quetiapine, ziprasidone and olanzapine. Now,

quetiapine and olanzapine are being proposed for both schizophrenia and bipolar mania, while ziprasidone, the application there is limited to bipolar mania.

The schizophrenia claims are all focused on the age range of 13 to 17, while, for bipolar mania for quetiapine and ziprasidone, the range is 10 to 17; for olanzapine, it's, again, 13 to 17.

I would point out that all three of these drugs are already approved for schizophrenia and bipolar mania in adults.

Now, each of these sponsors had conducted one acute placebo-controlled efficacy and safety trial for each of the indications for which they're seeking a claim. In addition, they have obtained pharmacokinetic data and some longer-term safety data in these populations.

Now, we have provided you all of FDA's review documents for these applications, as well as background packages from the three sponsors that support their claims.

The division has not yet reached a final

conclusion on these applications, but I can say that, in general, we are in agreement with the sponsors that the data tend to support that effectiveness claims that they are seeking. In addition to that, the safety profiles for these three drugs in the populations that were studied here appear to be qualitatively similar to what we're seeing in adults. There are some quantitative differences and some other differences that will be pointed out during the presentations.

It's important to acknowledge that both schizophrenia and bipolar disorder are serious illnesses in pediatric patients and represent a substantial burden both for patients and their families.

Now, at the present time, as you know, there are two antipsychotic drugs that are approved for the treatment of schizophrenia and bipolar mania in pediatric patients. Those drugs are risperidone and aripriprazol. Now, quetiapine, ziprasidone and olanzapine, if

approved for these indications would provide additional treatment options for these patients.

It's important to note that all three of these drugs, even though they are not yet approved for these claims, are being used by clinicians in treating these patients.

It's also important to point out that these drugs have significant risks, and these need to be considered, obviously, in deciding whether or not to grant these additional claims.

The adverse reactions that can occur with drugs in this class of antipsychotic drugs include, among others, somnolence, weight gain, increases in blood lipids and glucose, hyperprolactinemia, acute extrapyramidal symptoms and tardive dyskinesia.

It's important to note that even though we have very little data directly comparing these drugs, there appears to be some variability among them, quantitatively, with regard to certain of these risks. In fact, Dr. Vitiello in his comments will mention briefly an NIMH-funded

study, the TEOSS study, that did actually compare three antipsychotic drugs, two atypicals and one typical drug, and it did reveal distinct tolerability profiles for those three drugs.

It would actually be useful to have a study of the CATIE design in kids so that we could have a direct head-to-head comparison to look at the relative risks and benefits of these drugs in a pediatric population.

In any case, these risks are of particular concern in pediatric patients primarily because these arbitrary lifelong disorders, and these children would face many decades of taking these drugs.

There also is a concern about using them in the population because, of course, children are growing and developing, and they are viewed as being particularly vulnerable to the effects of these drugs for that reason, so we have to be very mindful of the risks of these drugs.

I would also note that, for two of these drugs, for quetiapine and olanzapine, the

pediatric safety findings are already incorporated into existing labeling. In fact, for Zyprexa, there's a medication guide which details the risks, both for adults and for pediatric patients.

I would also point out that Lilly has accepted the division's recommendation that if it were to be approved for its sought claims, that it would have second-line status because of the very prominent metabolic risks that we're seeing with olanzapine.

Now, in terms of the formal presentations, you're going to hear a summary of the safety and efficacy data from each of the three sponsors for their programs. FDA will not be making separate presentations since we are essentially in agreement with the sponsors on the data that they're going to be presenting. We worked with them, both on their background packages and the construction of their slides, and we're comfortable that what they're presenting fairly represents the data.

We have, however, asked Dr. Vitiello to

make some brief comments about the seriousness of schizophrenia and bipolar disorder in the pediatric population and the importance of having treatment options for these disorders.

Now, as I pointed out, the division has not reached a final conclusion on these applications and we seek your advice before we do reach a final judgment.

So after you've heard all the findings and the arguments, we will ask you to discuss and vote on questions regarding safety and efficacy for each of these claims. The questions will be the standard questions about safety and efficacy for each of the claims that are being sought.

Of course, you should not feel constrained by this set of questions. There may be other issues that you wish to discuss, and if you feel the need to modify the questions, you of course may do that, or you may pose other questions.

And I will stop there and turn the meeting back over to Dr. Goodman.

DR. GOODMAN: Thank you very much, Tom. Our next speaker is Dr. Ben Vitiello of National Institute of Mental Health.

DR. VITIELLO: Good morning. So this is just some introductory comments on early-onset schizophrenia and bipolar disorder. I have no financial relationship with pharmaceutical companies.

So for early-onset schizophrenia, we intend the schizophrenia which has four clinical onsets before age 18, meaning full diagnostic criteria are met before age 18 and not just prodromal syndrome. And this really accounts for about one-third of all cases of schizophrenia. It is estimated that the median age of onset of schizophrenia in males is in the early 20s, and for females is in the late 20s. So early-onset schizophrenia accounts for more cases of male schizophrenia than female schizophrenia.

Schizophrenia, by the way, is a very rare condition under age 13, so before puberty, it is extremely rare.

It's not a distinct disorder from adult schizophrenia. It's the same disorder, as various continuity of phenomenology and of treatment response. As for adults, pharmacological treatment is the only effective treatment for schizophrenia. And psychosocial intervention can be helpful for rehabilitation of the patient, addressing the dysfunction, but not for the symptoms of psychosis, per se.

So we use the same diagnostic criteria that we use for schizophrenia in general, including positive symptoms of delusions, hallucinations, disorganized speech and disorganized behavior, and negative symptoms, with changes in affect and in avolition.

The condition inevitably is accompanied by major dysfunction. It has a devastating, actually, impact on adolescents because, at that age, they are engaged in education, and so that is regularly disrupted and has really a negative impact on their development.

It also has a similar biological feature

because there is a progressive loss of cortical matter in the brain of adolescents that is evidenced by enlargement of the ventricles by the time that the diagnosis actually occurs.

And also there is continuity of treatment response because the data that are available so far are pretty consistent in showing that antipsychotic treatment is superior to placebo in controlling symptoms, especially positive symptoms, but also negative symptoms.

And besides for the fact that clozapine is proven better than other antipsychotics in direct comparison, there is no evidence of greater efficacy of other antipsychotic than each other; in particular, there is no evidence of a greater efficacy of second-generation antipsychotics over first-generation antipsychotics, except for clozapine, of course.

There are, however, some specific characteristics that don't make it a separate disorder, but beg attention to the characteristics of schizophrenia during adolescence, meaning

schizophrenia that has an early onset tend to have a more severe impact on cognitive functioning, and there is a progressive cognitive decline that is very often observed in these adolescents.

There is a severe functional impairment, so very few actually are able then to achieve full occupational status and end up quite often on disability.

And sometimes -- or quite often, actually, there is a response to antipsychotic that is not optimal, and the prognosis in general is worse than later-onset schizophrenia.

I want to present some data from the treatment of early-onset schizophrenia spectrum, or TEOSS, a study that was funded by the National Institute of Mental Health, and it was published in the American Journal of Psychiatry in December 2008. It was a study that was conducted at four university sites in the United States and that compared three different antipsychotics, olanzapine, risperidone and molindone -- molindone is a first-generation antipsychotic; olanzapine

and risperidone are second-generation antipsychotics -- in children and adolescents, primarily with schizophrenia. Most of these patients had schizophrenia, and some of them also, one-third, had schizo-affective disorder.

And this study -- it is not a large study, but I think it's quite informative in spite of a fairly modest sample size -- compared different antidepressants to each other. These are the doses, the mean final doses. You see they are not very high doses, but they are clearly therapeutic range doses.

And in this slide you can see the major flow of a patient in the study and also the outcome. And the first observation is that about -- between one-third and half of all the patients prematurely discontinued treatment either for poor response to the treatment they were randomized or because of adverse events.

So, you know, the first step of treatment for schizophrenia oftentimes result in premature discontinuation, and another antipsychotic needs

to be started.

And the second observation is of all the patients that were randomized, only about one-third to one-half had some significant benefit from the treatment, which is important. It's certainly clinically significant, but it's far from ideal, of course.

And responded here, or improvement, means a decline of 20 percent on their symptoms. So it doesn't mean cured. It means that their symptomatology was significantly reduced, and they were certainly improved at the level that was clinically significant, but were still suffering from schizophrenia.

The sample size, as I mentioned, is fairly small for a clinical trial, and does not really allow to distinguish in a statistically significant way the three treatments on efficacy outcomes. However, in spite of being fairly small, there was a statistically significant difference on the safety profile, and each drug actually presented with their own tolerability

profile in that olanzapine increased weight, cholesterol, insulin -- fasting insulin and liver enzymes more than other drugs. Other drugs actually did not. Or risperidone increased weight somewhat, but olanzapine has a significantly greater increase in weight.

This is a short-term study, eight weeks. And risperidone, on the contrary, increased prolactin, something that was not observed in the other two treatments, and molindone induced akathisia.

So, in conclusion, early-onset schizophrenia is a severe form of schizophrenia with major negative impacts on cognitive and social development that almost inevitably results in chronic functional impairment and is sometimes -- often, I would say -- difficult to treat. It requires multiple steps before arriving at a treatment that has some efficacy.

Some comments now on bipolar disorder, which is the other condition being considered here for labeling. There are different types of

bipolar disorder. Here we focused on bipolar disorder type I whose essential feature, from clinical phenomenology is mania, so a manic episode which is a distinct elevation or change in mood toward irritability that lasts for at least one week, plus some additional symptoms that I will mention, and which causes marked improvement -- impairment -- I'm sorry; here is a typo -- that causes marked impairment in functioning.

The other symptoms that must be present, you will see in this list, include grandiosity, decreased need for sleep, speech that is pressured and increased in quantity, flight of ideas, distractibility, increased activity and excessive involvement in pleasurable activities.

These are the same criteria that we use for adults, and we don't consider bipolar disorder in chid, generally speaking, as a distinct episode in terms of type I -- bipolar type I. However, you will see from this list that, developmentally, it's sometimes challenging to identify grandiosity

in adolescents and in children, and some symptoms like distractibility and increased activity are not really specific for bipolar, as can be found in other conditions, such as attention deficit disorder.

So the diagnosis of bipolar in children and adolescents requires careful attention to possible other conditions, and it is sometimes, again, you know, a challenging endeavor.

Bipolar disorder in the general population of type I has a lifetime prevalence of about 1 percent in adults. It's not really known with precision in adolescence. Some statistics indicate that it's as low as 0.1 percent. However, manic symptoms are much more prevalent, even though they don't necessarily translate into the marked impairment that is necessary to make the full diagnosis. And we don't really know what is the prevalence of bipolar disorder in prepubertal children at this point.

However, we know for sure, from an epidemiological study that bipolar disorder starts

in children and in adolescence. And we know, for instance, from studies like the Epidemiological Catchment Area study that was done in the '80s and published in the early '90s where the median age of onset of bipolar disorder in adults was estimated to be 19 years. And, retrospectively, these patients with bipolar disorder indicated that quite often the disorder got started earlier. And, actually, the highest hazard for developing the condition, highest risk, is between age 15 and 19, with a detectable risk also between age 5 of 9.

And this slide basically summarized what I have indicated where you have on the X the age group, and the hazard rate on the Y, and you can see that there are risks, which is identifiable as early as age 10, and even before.

So it does exist, and it certainly -- it is an important clinical condition that has a major impact on the life of these children.

I want to add also that there is a very lively debate currently among experts in child

psychiatry about the fact that the presentation of bipolar disorder may be somewhat atypical. This probably does not have an implication for the labeling and for the studies that we are reviewing today and tomorrow because they adhered to the sort of standard DSM full diagnosis of bipolar I. However, in the community, a diagnosis of bipolar disorder is sometimes given to children who don't really have a classic manic episode, but they are more characterized by chronic irritability with temper tantrums, severe temper tantrums, aggressive behavior, disinhibited behavior, and therefore they present either a continuous or a rapid cycling, as you prefer -- look at this, meaning several tantrums or cycles, affective storms, during the day or during the week, rather than an entire week of consistently elevated irritable mood.

So there are questions about different presentations of bipolar disorder in adolescents.

This phenotype that seems to be observed in children -- sort of atypical I will say --

seems anyway to be consistent with a mixed phenotype where you have symptoms of mania and major depression mixed up in the same episode, a sort of dysphoric mania, that seems to account for about 20 percent of adult cases of bipolar disorder, and is reported to have an early onset, a longer duration, and a more severe prognosis.

So there is some continuity, in any way, between children and adult bipolar, even with these mixed and atypical features.

Why is it important to diagnose and to treat bipolar disorder in childhood? First of all, it is a very disruptive condition that prevents children from -- oftentimes from attending school or anyway disrupts their education, their interpersonal relationships. It's a major challenge for parents and for teachers. And it increases the risk for suicide.

Early treatment may improve the prognosis, so treatment -- it's certainly recommended in the presence of bipolar disorder, and the treatment is primarily pharmacological;

that is, psychosocial intervention has more like an ancillary role in improving social skills, but they don't really go to the core symptoms of mania.

And the other reason for recognizing and properly treating it is that, if it's left unrecognized, some of these children may be treated with other medications, such as stimulants or antidepressants alone, which may not be appropriate for their condition.

Thank you.

DR. GOODMAN: Thank you very much, Ben. Maybe you could stay there for just a moment. I think we're doing very well on our schedule, and I was just wondering whether there might be any questions from members of the panel that are not pediatric mental health specialists about either childhood-onset schizophrenia or bipolar disorder.

And I want to comment -- I'm very glad that you raised the issue about so-called atypical or mixed bipolar disorder. I think that's one of the issues we'll want to be -- grapple with,

whether there would be some drift in prescribing in areas that are not necessarily exactly -- strictly defined as in a DSM, and whether or not there might be some increase in prescribing in ares that are sort of at the margins of bipolar disorder.

So are there any questions from panelists for either Ben or other experts on our panel about these conditions or their treatment? Dr. Temple?

DR. TEMPLE: Actually, I have one about the TEOSS trial. For fairly obvious reasons there was no placebo control group in there. I wonder if you have some thoughts about what you can say about effectiveness in the absence of a placebo. How much of the response that was seen there could have been spontaneous improvement in those people? Do you have any thoughts about that?

DR. VITIELLO: Well -- yes, the absence of a placebo is certainly a methodological limitation which -- one should never discount the so-called placebo response or spontaneous, basically, fluctuation in symptoms. Having

personally been involved in this study as a co-investigator and having gone through the clinical description of these patients, I have to say this is very severe -- these were very severe patients. Oftentimes they have failed other treatments. They went on suffering from the condition for several months, because we followed them up for a total of one year. I doubt that, even though spontaneous changes in phenomenology and symptoms is -- it's a rule, I think anyway that any placebo impact would have been very, very small.

I cannot emphasize how severe these patients were. One patient committed suicide. They were very, very impaired, so -- again, you know, I think that we seek here I feel fairly confident is an effect of the medication.

DR. GOODMAN: Dr. Grady?

DR. GRADY-WELIKY: Ben, I was wondering if you could just speak a little bit more to the debate around the atypical nature of bipolar disorder in children and how much of the symptoms

that you describe here could just be normal adolescent behavior. Is it really out of the range of normal that we're talking or -- what's the debate really about, because I have concerns about that?

DR. VITIELLO: Yes. To answer your question, it is out of a range of normal behavior for age. So there is no question that this is a psychopathology. The question is what type of psychopathology? And that what's the debate is.

But nobody doubts that these are kids who suffer from a condition which is an emotion condition, a mood disorder, and they're very impaired.

Actually, I would ask, Ken, if you could comment because you work, really, on this, and you are supposed, actually, to give this talk -- for the reason that you know, you are not able to, but if you could comment on this.

DR. TOWBIN: I'd be delighted to, and I think the question actually goes -- and echoes some of the earlier comments that Wayne made. I

think that we will need to be very careful in thinking about what might be regarded as narrow phenotype bipolar disorder which is characterized by an episodic course in which there is a distinct change in mood from the child's baseline, and this more -- what is in the community sometimes called bipolar disorder which is characterized by chronic irritability and hyperarousal symptoms, often accompanied by oppositional defiant kinds of behaviors and symptoms that go along with attention deficit hyperactivity disorder.

I think one of the things that the committee will have to think carefully about is how we would view the application of these powerful antipsychotic medications into a population of children who have high levels of irritability and attentional problems.

That being said, ours is a group that does study both what we regard as this severe mood dysregulation condition, being not yet certain that it should be included under the so-called bipolar label. And our sense is, and the

individuals that we see in our program, their level of functioning is as severely impaired as those with acute mania and bipolar disorder. So we are not talking about a level of kind of ordinary development or a child who is sassy to their parent, but really individuals who are impaired across different domains of functioning.

I think the issue for us is going to be whether individuals who have attention deficit hyperactivity disorder and high levels of irritability are a group that would be appropriately treated with these kinds of agents.

DR. GOODMAN: Dr. Towbin, do you see any measures that could be taken in order to educate practitioners in how to make that differentiation?

DR. TOWBIN: Well, I think that there are a number of measures that might be taken. Of course I think having good information about this distinction is important. One of the other things that work is proceeding on is looking at the natural history of this, and indeed it does appear that individuals with this more chronic course and

irritability end up being adults with depression or anxiety disorders, rather than adults with bipolar disorder, whereas this kind or narrower group that has episodic changes in mood does, in the long run, end up looking more like adult bipolar disorder. So I think helping practitioners understand that distinction may be useful in thinking about prescribing guidelines.

DR. GOODMAN: I'm going to allow myself one more follow-up question for Dr. Towbin. In those cases where you've done your best job to try to differentiate whether it's the narrowly defined phenotype of bipolar disorder or this kind of mixed irritability chronic one, but you feel that it warrants intervention, warrants pharmacotherapy, what would you ordinarily start with?

DR. TOWBIN: Well, since we don't have nearly the quality of a trial like the TEOSS trial for schizophrenia in this population, I think we have to recognize that this severe mood dysregulated population is quite heterogenous.

Many of these, for example, are individuals with attention deficit hyperactivity disorder and very high levels of anxiety, which can produce quite a bit of irritability.

And so chasing irritability might lead you to using antipsychotic medication rather than thing that might be appropriate treatment for anxiety and for attention deficit hyperactivity disorder, such as stimulants and serotonin reuptake inhibitors.

Ben's point earlier about how, if you think about these individuals as having bipolar disorder, would take you 180 degrees from that direction. And so thinking about the differential diagnosis of extreme irritability is going to be crucial. And, indeed, pharmacological agents like stimulants can reduce irritability in children with ADHD. Certainly serotonin reuptake inhibitors can reduce irritability in individuals with anxiety and depression.

DR. GOODMAN: How about the role of mood stabilizers, anti-epileptic medications, lithium?

DR. TOWBIN: In this population, we did perform a study, a double-blind placebo-controlled trial of lithium carbonate in individuals who had rigorously defined severe mood dysregulation a priori criteria that we had established for it, and we found that lithium was no better than placebo in that population.

DR. GOODMAN: Dr. Granger, you had a question?

DR. GRANGER: Yes. There's some interesting information in the briefing document about the use of the three drugs in children and adolescents, but can you give us an idea, for these two indications, what proportion of patients now approximately are being treated with the three drugs that we're reviewing versus some of the others, risperidone or other drugs?

DR. GOODMAN: Maybe the FDA has that answer. I'm not sure. Dr. Vitiello has --

DR. VITIELLO: I think the briefing material included some estimates of use based on the IMS database. I think I saw that there were

some estimates of use in the community for these drugs for the 2004 and 2008. So it's part of the material that was made available for the --

DR. GOODMAN: Anybody have their finger on that?

DR. GRANGER: The briefing information has the information for these three drugs, but not for other drugs, at least not the way --

DR. VITIELLO: Oh.

DR. GRANGER: Not what I saw. I'm just wondering, is the bulk of pharmacologic therapy for these conditions the three drugs that we're talking about today or is there a substantial use of other -- for example, the two currently approved drugs?

DR. VITIELLO: Certainly risperidone is probably the most widely used right now drug, and also has been the most studied drug, and the earliest studied drug in children. It has three indications: schizophrenia, age 13 to 17; bipolar, age 10 to 17; and irritability in the context of autism, age 6 to 17. So risperidone is

the most commonly used drug.

Also, I can tell you that all the indicators point to an increased use of these drugs in the early 2000s, but the numbers for the last two or three years seem to indicate that this use has been leveling off and is not further escalating, at least in the last couple of years.

DR. GOODMAN: Okay. If there are no more questions, we'll proceed with the agenda.

I'd now like to start with the industry presentations, beginning with AstraZeneca Pharmaceuticals. I'd like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at specific request of the panel.

And we have a series of presentations. Unless there is something really burning, I'm going to ask the committee to withhold their questions until all the presentations are given. If you have something that you really feel needs to be answered, just let me know.

DR. RAK: Good morning. Thank you, Dr. Vitiello, for that presentation to start the proceedings today. My name is Ihor Rak, and I'm vice president of clinical neuroscience at AstraZeneca. AstraZeneca is pleased to be here today to review the quetiapine clinical development program in two serious psychiatric disorders in children and adolescents. Presently, there are few approved treatment options.

We will present the efficacy and safety data for both the treatment of acute bipolar mania in 10- to 17-year-olds and the treatment of schizophrenia in adolescents.

Quetiapine has benefitted many adults with bipolar mania and schizophrenia. The clinical data in the pediatric program we will review today supports quetiapine as a valuable treatment option for children and adolescents with mania or schizophrenia.

As we heard from Dr. Vitiello's presentation, mania and schizophrenia are extremely serious and debilitating diseases in

children psychiatry. They cause substantial chronic suffering to affected children and their families. These disorders interfere with normal development and the acquisition of fundamental skills necessary to become functioning adults.

Often, schizophrenia and mania first present in adolescents and young adults, and it is commonly accepted that delaying treatment is associated with an increased burden of disease, such as suicide attempts and completions.

Pharmacologic intervention is an integral part of treatment of these diseases. Antipsychotics are recommended as first-line treatments for both schizophrenia and mania by the treatment guidelines from the American Academy of Child and Adolescent Psychiatry.

The treatment guidelines recommend switching medications in case of poor response or intolerability. Very few treatments are currently approved for children and adolescents with mania or schizophrenia, and many children and adolescents do not respond to these first-line

treatment options.

However, there are many more currently approved medications available to adults. Importantly, the currently approved medications have been shown to bring significant benefits to adults with these serious disorders.

As pointed out in the memorandum by Dr. Laughren and discussed earlier today, these drugs, although not yet approved for these disorders in pediatric patients, are nevertheless used in treating these patients.

Since different medications have different safety and tolerability profiles, availability of multiple approved medications can increase the likelihood of benefit for more children and adolescents with schizophrenia and mania.

AstraZeneca submitted the two supplements shown here after a formal written request from the FDA issued in February of 2003. The FDA has indicated that they believe a sufficiently strong case has been made for continuity between adult

and pediatric patients with both schizophrenia and bipolar disorder to permit pediatric claims for a drug already approved in adults.

Quetiapine is approved in over 90 countries for the treatment of adults with schizophrenia and bipolar disorder. The key safety data observed in these pediatric studies has been added to the Seroquel U.S. prescribing information, and that's in your appendix D in the briefing document.

On 23rd January of 2009, the FDA informed AstraZeneca that the supplements met the requirements of the written request. The clinical experience for more than 26,000 patients in our clinical study database, which includes approximately 500 pediatric patients, as well as experience from more than an estimated 22 million patients treated worldwide is important to consider as we review the data from quetiapine clinical studies in children and adolescents with mania or schizophrenia.

This is our agenda today. Dr. Hans

Eriksson will review the efficacy demonstrated in both pediatric mania and schizophrenia. Dr. Liza O'Dowd will review the general short and longer-term safety of quetiapine with specific emphasis on topics of interest in children and adolescents. I will then review the risk management plan. We will then ask Dr. Lili Kopala, clinical professor of medicine and psychiatry at the University of British Columbia, to speak to the clinical use of antipsychotic medications in the treatment of these serious psychiatric disorders in children and adolescents. I will then conclude with the benefit-risk assessment and answer clarification questions.

AstraZeneca is also very pleased to be accompanied today by several external advisors, as shown here. Now I'll turn the podium over to Dr. Eriksson.

DR. ERIKSSON: Good morning. My name is Hans Eriksson. I'm a clinical psychiatrist and I'm the global medical lead for Seroquel with AstraZeneca.

Today I will discuss the efficacy of quetiapine in the treatment of mania in children and adolescents and in the treatment of schizophrenia in adolescents. I will provide an overview of the clinical development program, and then I will discuss some of the individual studies in more depth.

As already mentioned by Dr. Rak, the clinical development program was based on a written request from the FDA, and it was conducted in agreement with the agency's view. It consisted of four studies. Study 28 was a pharmacokinetic study in a pediatric population with mania and schizophrenia. Two different daily doses were studied at steady state, 400 and 800 milligrams.

The results are described in the briefing document, and will only be referred to briefly in this presentation.

There were two randomized placebo-controlled short-term studies designed to assess efficacy and safety in mania and schizophrenia, respectively. The mania study,

study 149, included children and adolescents from 10 to 17 years of age, and had a duration of three weeks. Two daily doses were studied, 400 milligrams and 600 milligrams.

The schizophrenia study, study 112, included adolescents from 13 to 17 years of age, and had a duration of six weeks. Also here, two daily doses were studied, but in this case, 400 and 800 milligrams.

There was also a longer-term safety study, study 150, and this study recruited patients who had completed either the mania or the schizophrenia study, and here the dose range was 400 to 800 milligrams per day, and the duration was up to 26 weeks, and this study had an open-label design.

One very important question you need to consider before exploring a drug in a younger population is what dose to select, and the dose rationale was built on several pieces of information. First, the dose range of 400 to 800 milligrams per day is very well established as

being generally safe and efficacious in adults with mania and schizophrenia. Second, the pharmacokinetic study of quetiapine in children and adolescents demonstrated a pharmacokinetic profile similar to what is seen in adults.

Third, we obtained extensive input from practicing child and adolescent psychiatrists who are familiar with quetiapine. And, fourth, these doses had been explored in previous pilot studies.

So based on this overall understanding of the dose, we decided to explore the doses of 400 and 600 milligrams in mania and 400 and 800 milligrams in schizophrenia.

To understand improvement in patients, it's important to assess general functioning. In the pediatric population, this can be measured using the Children's Global Assessment Scale, which I will refer to as C-GAS. On this scale, which is not specific for a certain disease, a score of 100 represents superior functioning, while a low score of 1 represents individuals in need of constant supervision.

The young patients we studied in this program had a mean C-GAS score at inclusion of approximately 45 in the mania study and approximately 43 in the schizophrenia study. And here we can see that a score between 41 and 50 corresponds to a moderate degree of interference in functioning in most social areas or severe impairment of functioning in one area.

And the reason that I emphasize the baseline value of C-GAS, which only was a secondary efficacy end point in the study, is to help in the understanding of the clinical characteristics of these seriously ill pediatric patients.

I will now discuss the efficacy results from the study conducted in children and adolescents with mania. In this study, patients who had been screened for inclusion had their prior treatment washed out before they were randomized to one of three treatment arms: 400 milligrams per day quetiapine; 600 milligrams per day quetiapine; or placebo. And the treatment

duration was three weeks.

The primary outcome in this study was the change in the Young Mania Rating Scale score from baseline to day 21 compared to placebo. This is a well-established primary measure in efficacy studies in mania and it's the most widely used scale for efficacy assessments in adult as well as in pediatric patients, and I will refer to this scale as YMRS.

It measures the severity of different components of the manic syndrome, and it has 11 items, including core features of mania, such as elevated mood. Each item can be scored from zero to 4 or, in some instances, 8, giving an overall range of zero to 60, with a higher value representing higher severity. And the mean baseline score in studies in mania in adults is typically around 30. And to be included, patients often need to have a score of 20 or higher. Remission is often defines as reaching a score of 12 or lower.

Several other parameters were also

assessed, and among the secondary outcomes were response, defined as at least a 50 percent improvement in the YMRS score; remission, defined as reaching a YMRS score of 12 or less; change in the C-GAS score -- and this is the functioning scale I just mentioned; change in the score on the Clinical Global Impressions Scale for bipolar disorder, or CGI-BP for severity, as well as the proportion of patients assessed as much improved or very much improved at day 21 on this scale.

The CGI-BP scale is important because it provides a method to translate the clinician's overall assessment of the individual patient into a score.

To be included in this study, the patients had to be from 10 to 17 years of age and have mania as a component of bipolar I disorder. The diagnosis also had to be confirmed using a semistructured interview instrument that is often used in child and adolescent psychiatry that is called K-SADS-PL.

A diagnosis of attention deficit

hyperactivity disorder, or ADHD, could be present as long as it was not the primary diagnosis. The YMRS score had to be at least 20.

Among the exclusion criteria were another clinical psychiatric disorder from DSM axis 1, except ADHD, but also mental retardation, serious suicidal or homicidal risk or a medical comorbidity.

Psychostimulants were allowed, but only if the dose had been stable for at least 30 days before screening.

393 patients were enrolled, and 284 were randomized. There were almost 100 patients in each treatment arm. There were more withdrawals due to adverse events in the quetiapine-treated arms, but overall more quetiapine-treated patients completed the study, and the completion rate was from 72 to 82 percent which, for a study in mania, is a very good figure. We can also see that, overall, more than 70 percent of the patients continued into study 150, which was the open-label study.

And here we can see some of the characteristics at baseline for the patients participating in this study. There were more boys than girls. The mean age at inclusion was about 13 years, with a little less than half of the patients in the age range 10 to 12 years. The mean weight was 61 kilograms, and 45 percent of these patients had comorbid ADHD. The mean YMRS score at inclusion was approximately 30. And the mean C-GAS score was 45, as I've already shown you.

This table shows the effect -- shows the results for the primary efficacy variable, YMRS total score change from baseline to day 21, analyzed using mixed model repeated measures, or MMRM, with baseline YMRS total scale as a covariate.

As you can see in the yellow box, the change from baseline to end point at day 21 was significantly better for both doses, 400 and 600 milligrams per day, compared with placebo, 5.2 points and 6.6 points on the YMRS scale,

respectively. This difference, versus placebo, is not only statistically significant, but also clinically relevant and meaningful for a young patient with mania.

This slide shows the change in total YMRS score over time in the three treatment arms during the three weeks with placebo-controlled treatment. We can see that both doses separate from placebo from day 7 and, at end point, the 600 milligram per day dose arm has a somewhat larger numerical separation from placebo than the 400 milligram per day dose arm. And below the graph the number of patients contributing to each data point is indicated.

This part of the slide shows what happened during study 150, which had an open-label design. So if a patient is coming from the two quetiapine arms of study 149 and continuing into the open-label study, as shown by the red dotted line, the improvement was maintained over time, measured as mean YMRS score.

We can also see that the patients who had

received placebo during study 149 and were switched to quetiapine in the open-label phase. They had a numerical improvement of their YMRS score, as shown by the dotted gray line. However, it should be recognized that there was no comparator arm in study 150, which was primarily a safety study.

Significant effects were seen for a number of secondary outcome measures for both doses compared to placebo. For response, as well as for remission, both the doses 400 and 600 milligrams per day were superior to placebo. CGI-BP was used to assess overall severity of illness and global improvement. A significant effect was seen both for decreasing severity of illness and for the proportion of patients who were much improved, or very much improved. The improvement in C-GAS score was also statistically superior to placebo for both doses.

Not shown here is that the efficacy of quetiapine was not affected by comorbid ADHD or psychostimulant use, nor was it different between

children and adolescents.

So to summarize the efficacy results in mania in children and adolescents, we have demonstrated efficacy for quetiapine 400 and 600 milligrams per day on the primary efficacy measure, change from baseline in YMRS total score. We have also shown efficacy on several secondary measures.

Most mania patients achieved clinical response during this three-week acute study, and during longer-term open-label treatment, the improvement seen during double-blind treatment was maintained.

And I will now turn to the efficacy study conducted in adolescents with schizophrenia. In this study in schizophrenia, adolescent patients had their prior treatment washed out before they were randomized to one of three treatment arms; in this case, 400 milligrams per day quetiapine, 800 milligrams per day quetiapine, or placebo. And the treatment duration in this study was six weeks.

The primary outcome in this study was the change in the positive and negative syndrome scale score from baseline to day 42 compared to placebo. And this scale has been extensively used for the primary measure in efficacy studies in schizophrenia. Today it is the most widely used scale for efficacy assessments in schizophrenia studies in adults and in pediatric patients, and I will refer to this scale as PANSS.

The scale has seven items for positive symptoms, like delusions and hallucinations, seven items for negative symptoms, like emotional withdrawal and blunted affect, and 16 general psychopathology symptom items. And the score can be from 30 to 210, with a higher value indicating higher severity. And a PANSS score of about 95 is considered to represent the patient being markedly ill.

Several other parameters were also assessed, and among the secondary outcomes were response, which was defined as at least 30 percent improvement in the PANSS score, change in C-GAS,

which is the functioning scale we discussed earlier, change in the Clinical Global Impression Scale for severity as well as for improvement.

To be included in this study, patients had to be from 13 to 17 years of age and have schizophrenia confirmed by the K-SADS-PL diagnostic instrument, and the PANSS score at inclusion had to be at least 60. And for the subitems of delusions, conceptual disorganization and hallucinatory behavior, the rating had to be at least 4, meaning moderate severity.

Among the exclusion criteria were a number of other psychiatric disorders including bipolar disorder, but also mental retardation, serious suicidal or homicidal risk or a medical comorbidity.

268 patients were enrolled, and 222 were randomized. There were approximately 75 patients in each treatment arm. There were more withdrawals due to adverse events in the quetiapine-treated arms, but overall there were more study completions in the quetiapine arms than

in the placebo arm.

This was mainly because of the development of study-specific discontinuation criteria for placebo-treated patients, reflecting a worsening of symptoms.

63 to 82 percent of the patients completed the study, and for a study in schizophrenia, this is a good completion rate. And we can also see that, overall, almost 80 percent of the patients continued into the open-label study, study 150.

And here we can see the characteristics of the patients participating in this study. There were more boys than girls. The mean age at inclusion was close to 15-1/2 years. The mean weight was 62 kilograms. And 10 percent of these patients had comorbid ADHD. The mean PANSS score at inclusion was approximately 96, which is a score that reflects marked severity of illness. And as you have already seen, the mean C-GAS score at inclusion was 43.

This table shows the results for the

primary efficacy variable, PANSS total score change from baseline to day 42, analyzed using mixed model repeated measures, MMRM, with baseline PANSS total score as a covariate. And as shown in the yellow box, the change from baseline to end point at day 42 was significantly better for both doses compared with placebo, 8.2 points and 9.3 points on the PANSS scale, respectively. And this difference versus placebo was clinically relevant and meaningful for a young patient with schizophrenia.

Here we see the change in total PANSS score over time in the three treatment arms during the six weeks with placebo-controlled treatment. At end point, both doses separated from placebo, and for the higher, 800-milligram dose, a statistical separation from placebo was seen from day 14, but overall, there was little difference between the two quetiapine dose arms.

This part of the slide shows what happened during study 150, which had an open-label design. So for patients coming from the two

quetiapine arms of study 149 and continuing into the open-label study, as shown by the dotted red line, the improvement was also here maintained over time, measured as PANSS total score. We can also so that, in this study, patients who had received placebo during study 149 and were switched to quetiapine in the open-label phase, they had a numerical improvement of their PANSS score, as shown by the dotted gray line. But once again I'd like to remind you that there was no comparator arm in the open-label phase.

And I will now discuss the effects on a number of secondary outcomes. A higher proportion of patients were responders to treatment in each of the quetiapine groups compared to placebo, but this difference did not reach statistical significance. For the 800 milligrams per day dose arm, a statistically significant effect compared to placebo was seen on the Clinical Global Impression Scale for severity of illness as well as for global improvement. And for the 400 milligrams per day dose arm, a statistically

significant effect was seen for global improvement.

For 800 milligrams per day, the improvement in C-GAS score was also statistically superior to placebo, reflecting an improved general functioning.

So to summarize the efficacy results in schizophrenia in adolescents, we have demonstrated efficacy for quetiapine 400 and 800 milligrams per day on the primary efficacy measure, change from baseline in PANSS total score. Efficacy was also shown on secondary measures, and about half of the schizophrenia patients were much improved or very much improved on the CGI global improvement scale. And during longer-term open-label uncontrolled treatment, the numerical improvement seen during double-blind treatment was maintained.

So in overall summary, efficacy has been demonstrated for quetiapine in mania in children and adolescents and in schizophrenia in adolescents. Improvements on primary efficacy variables were supported by effects on secondary

variables, including general functioning. During longer-term open-label treatment, efficacy measures were maintained.

The efficacy of quetiapine shown in these two short-term studies in mania and schizophrenia is considered to be clinically relevant and meaningful. We have seen today that quetiapine, a drug with proven efficacy in adults, has a similar efficacy with a similar treatment effect in a younger population. We use the same doses and assess the patients using the same primary outcome variables as for adults.

So taken together, this establishes efficacy of quetiapine in these two debilitating disorders in pediatric patients.

I will now turn the podium over to Dr. Liza O'Dowd.

DR. O'DOWD: Good morning. My name is Liza O'Dowd. I'm vice president for late development in neuroscience at AstraZeneca. Today I will be discussing the safety data from the pediatric development program that you've just

heard about from Dr. Eriksson. Today's presentation will cover four broad categories of data, including adverse events -- including a discussion of specific adverse events, including sedation, extrapyramidal side effects, or EPS, and suicide, vital sign data, including heart rate, blood pressure and weight, laboratory data focusing on lipids, glucose and prolactin, and ECG data.

Additional information on other topics are provided for your review in the U.S. prescribing information as well as in the briefing document.

Today I will show you that quetiapine is generally well tolerated in children and adolescents ages 10 to 17 in short- and longer-term studies of up to 26 weeks. There are few differences across safety parameters noted when we consider the two indications of mania and schizophrenia, the children ages 10 to 12 and the adolescents ages 13 to 17, or the doses of 400 to 800 milligrams per day.

Importantly, for most safety parameters, the data in the pediatric patients were similar to those described for adults in the U.S. label which reminds us that children and adolescents are susceptible to the same potential risks of quetiapine exposure as adults, just as they experience similar efficacy.

Today I will also highlight areas where differences have been observed between pediatric patients and adults. These have also been addressed in the label.

As we have just reviewed with Dr. Eriksson, the pediatric program included two placebo-controlled short-term studies of three and six weeks' duration and a longer-term uncontrolled open-label study of 26 weeks' duration.

In evaluating the pediatric safety data, we have examined the data by looking within and between studies by indication, age and dose. In general, the safety findings are very consistent across these different categories. Therefore, to simplify today's presentation as well as to allow

a more precise characterization of the magnitude of observed changes, for most parameters discussed today, data from the two short-term studies have been combined and are presented as a short-term safety data pool.

Data for patients who continued into study 150 provides the longer-term safety data. In the data slides that will follow when discussing study 150, we will show you the two cohorts of patients, those previously treated with placebo and those previously treatment with quetiapine in the short-term studies. It's critical to remember, though, that all patients were treatment with quetiapine in study 150.

These studies were not powered to look for any particular adverse event, so only descriptive data will be presented here.

We will start with a review of adverse events. This table shows a summary of adverse events, and I'd like to draw your attention to a few important observations. Overall, common adverse events, serious adverse events and

discontinuations due to adverse events were more commonly reported for quetiapine compared to placebo. There was no apparent dose response for these categories of events.

Although there were some numerical differences in specific adverse events reported for younger patients compared to older patients, there were no apparent differences in the types of events experienced. These details can be found in your briefing document.

Importantly, there were no deaths in the pediatric program for any cause.

The common adverse events report in the short-term studies are summarized here by dose. I'd like to point out a few things. First, these events are very similar to those described for adult patients in the U.S. label, with no unexpected adverse [sic] seen in the pediatric patients. Overall, somnolence was among the most frequently reported adverse events for quetiapine, a finding which we also see in adults. I will discuss these events in detail in a moment.

One difference from the adult population is that increased appetite was reported more frequently in these short-term studies compared to the adult studies. In adult studies, these were reported as an infrequent adverse event, meaning with the frequency of less than one in a hundred.

A second observation is that over the dose range of 400 to 800 milligrams per day, there was little evidence of a dose response for most adverse events, with the exception of dry mouth and perhaps tachycardia.

Finally, we looked at common adverse events in patients with bipolar mania versus schizophrenia, children versus adolescents and in the short versus the longer-term studies. Within each of these comparisons, the findings were generally similar.

Now I'll return to the topic of somnolence. As I've just reviewed, somnolence was the most frequently reported adverse event and was the most common adverse event leading to discontinuation in the short-term studies,

occurring in 12 quetiapine patients, compared to one placebo patient. I'd like to characterize these events in more detail.

Events were rated as mild if they were easily tolerated, moderate if they interfered with normal activity, and severe if they were incapacitating. Most events of somnolence were reported as mild to moderate in intensity, with 6.5 percent reported as severe.

77 percent of events were reported in the first two weeks of treatment, suggesting that this is an adverse event that occurs early and is less likely to be reported for the first time later in treatment. The median duration of the event was 10 days for those reporting the event on placebo, and 12 days for those on quetiapine.

This pattern is consistent with what is seen in adults, where these events are reported early, and patients tend to develop tolerance to the sedative effects of quetiapine over time.

The next type of adverse event I will discuss are those related to extrapyramidal

symptoms and tardive dyskinesia, or EPS and TD. The potential for these events is clinically important as tardive dyskinesia in particular can be a serious and irreversible condition. There were no cases of tardive dyskinesia reported in either the short- or longer-term studies.

Looking at individual adverse events contributing to the overall assessment of EPS, we can see that all are reported at a rate of 4.1 percent or lower for quetiapine. Akathisia was one of the most common events, reported at a rate of 4.1 and 1 percent in quetiapine-treated patients with schizophrenia and mania, respectively.

EPS events were reported less frequently overall for the bipolar patients, compared to the schizophrenia patients. The quetiapine-placebo difference was approximately 8 percent for schizophrenia and 2 percent for the bipolar study. All of the cases report as mild to moderate in intensity, with the exception of one case. This case was a case of restlessness of severe

intensity where a patient was non-compliant with study medication. The event resolved when the patient was restarted on quetiapine.

There were no discontinuations in the short- or the longer-term study related to EPS side effects.

As with all other drugs with an indication in depression, quetiapine, approved for bipolar depression in adults, has a boxed warning for suicidality. In order to investigate our data thoroughly, we have used the Columbia Suicide Analysis methodology, a method recommended by the FDA and accepted to evaluate suicidality. In this clinical program, there were no completed suicides.

The data shown here displays events possibly related to suicide, according to the Columbia methodology. The top row is a summary of events that include suicide ideation, attempts or completed suicide. There was an imbalance of events for quetiapine compared to placebo at five versus zero, with three of the events in children

and two in adolescents.

In a broader evaluation of events, which includes cases where there is insufficient information to rule out suicide attempt, the findings were similar, with six events reported for quetiapine and two additional events reported for placebo patients.

Because there were few events in the program, it is difficult to draw further conclusions. However, as noted in the FDA's briefing materials, the difference between quetiapine and placebo were not statistically significant.

Overall, reported adverse events were generally consistent with those observed in quetiapine adult schizophrenia and bipolar mania studies, with the exception of increased appetite which was reported more frequently. Importantly, there were no unexpected adverse events.

As in adults, somnolence was the most frequently reported adverse event. These events were reported early in the course of studies and

were not dose-related.

EPS was reported with a low frequency, and there were no discontinuations due to EPS. Also, there were no cases of tardive dyskinesia. Overall, there were few events meeting the criteria for suicide attempt or ideation, with no completed suicides. Quetiapine's label includes class labeling for suicidality.

The next part of the presentation will summarize vital sign findings in the pediatric program. I'll be talking about mean increases and shifts in heart rate, blood pressure, absolute weight and changes in BMI Z scores. Before we begin, let me first refresh you on how patients were enrolled in the longer-term study, 150. The short-term studies are shown here on the left. The start of these studies is referred to as the double-blind baseline during the rest of this presentation. Patients treated with either quetiapine or placebo from study 112 and 149 were then able to enter study 150 for up to 26 weeks where all patients received quetiapine. This is

shown on the right.

In the data slides that will follow when discussing study 150, we will show you two cohorts of patients, those previously treated with placebo and those previously treatment with quetiapine in the short-term studies. The start of study 150 will be referred to as the open-label baseline.

This graph displays mean changes and standard deviations in supine heart rate over time. Quetiapine is plotted in pink and placebo in gray. During the short-term studies, mean increases in heart rate of 7.6 beats per minute were seen for quetiapine. As you can see, there's a great deal of variability in the data. The children had made greater mean increases in heart rate, 12.4 beats per minutes, compared to the adolescents of approximately 6 beats per minute, as was provided in the briefing document.

In the longer-term studies, mean changes for the overall population were less, approximately five beats per minute. To put the mean changes into perspective, the magnitude of

these changes are consistent with changes seen in adults for the overall population. In adults, the increases in heart rate of 7 beats per minute observed in clinical studies are believed to be due to alpha-adrenergic blockade.

Shifts in heart rate greater than 120 beats per minute in children and greater than 110 beats per minute in adolescents or an increase in heart rate of greater than 15 beats per minute were examined. Shifts in quetiapine were more frequent for quetiapine compared to placebo. Children experienced more shifts on quetiapine compared to the adolescents.

In the quetiapine program, supine and standing blood pressure were assessed. In the short- and longer-term studies, mean increases in systolic blood pressure were seen for the quetiapine patients compared with placebo. This graph displays mean changes in systolic blood pressure over time. Quetiapine is plotted in pink and placebo in gray. Overall, the changes were less than 2 millimeters of mercury at the end of

double-blind treatment and 1.7 millimeters of mercury at the end of open-label treatment. The main changes do not appear to progress over time.

As we saw for heart rate, there's a great deal of variability in the changes. Similarly, this graph shows results for diastolic blood pressure. Mean differences between quetiapine and placebo were smaller than seen for systolic blood pressure. For both systolic and diastolic blood pressure, there were differences noted by age, with mean increases from double-blind baseline in systolic blood pressure of 4 millimeters of mercury for children compared to 1 millimeter of mercury changes for adolescents at the end of study 150.

The definition of what constitutes a normal blood pressure in children and adolescents is obtained from nomograms based on age, gender and height.

We looked at children and adolescents who had elevated supine blood pressure at any time in three different ways. The first was using an

absolute threshold for a given age and gender adapted from these nomograms. The second was to look at increases in systolic blood pressure of 20 millimeters of mercury or more. And the third was to look at children and adolescents who had increases in blood pressure over the 95th percentile of normal, based on their individual criteria derived from the nomograms.

In the short-term studies, more patients on quetiapine compared to placebo experienced shifts in systolic blood pressure. The proportion of shifts were higher for the children compared to the adolescents. Interestingly, there was less variability in the proportion of patients identified as a shifter when comparing the three definitions for adolescents as opposed to those used to evaluate the children.

Findings were similar for diastolic blood pressure, with more shifts for quetiapine compared to placebo and for the younger patients compared to the older patients. Many patients in both treatment groups met the criteria for a 10

millimeter of mercury increase in diastolic blood pressure, although more quetiapine than placebo patients did meet this criteria.

The highest systolic blood pressure we observed in short or longer-term studies was 160 over 80.

The etiology of these blood pressure observations in pediatric patients is not fully understood. In adults, in fact, the primary blood pressure finding observed in clinical studies is orthostatic hypotension, thought to be due to alpha-adrenergic blockade.

We will now discuss weight, which was assessed at each visit. Patients on quetiapine had a 1.65 kilogram mean weight increase compared to 0.08 kilograms on placebo in the short-term studies.

This table presents data for all patients in study 150 and divides them into two cohorts, those that had received placebo or those that had received quetiapine in the short-term studies.

Changes from the double-blind baseline

are shown, which shows a total weight change over the duration of the short- and long-term studies, as well as from open-label baseline which shows the additional changes in weight just seen during the open-label study period.

About 40 percent of the total weight gain occurred in the first three to three six weeks of the short-term studies, while the rest of the change of weight, approximately 3 kilograms, occurred over the length of 26 weeks in study 150.

For patients previously treated with placebo, the total weight gain of 5 kilograms was similar to the total weight gain experienced previously treated with quetiapine.

In the short-term studies, we examined shifts in weight by looking at patients who had increases in their weight of more than 7 percent from baseline. 17 percent of quetiapine and 2.5 percent of placebo patients met this criteria.

Rate of growth and weight gain varies through childhood and adolescence and between boys and girls. What is considered a normal BMI varies

until final height is obtained. Therefore, in the longer-term pediatric studies, it is not sufficient to solely look at changes in BMI or weight. Rather, it is necessary to adjust for a child's age, gender and changing height. One way to do this is an analysis of BMI Z scores. A Z score is a calculated deviation from the population mean, which are obtained from gender and age-based nomograms obtained from the CDC.

A child with a Z score of zero has the same BMI as the population mean, while a child with a Z score of 0.5 is 0.5 standard deviations heavier than the population mean.

This graph demonstrates the changes in BMI Z score over time. In the short-term studies, BMI Z scores increased for quetiapine but not for placebo. There were small additional increases in Z scores for those who continued on quetiapine in study 150. You can also see that patients previously treated on placebo also had increases in BMI Z score.

Mean changes in Z score tended to plateau

over the length of the study, particularly from week 16 on for those previously treated with quetiapine. The total change from double-blind baseline was approximately 0.2 standard deviations, a finding consistent with the pattern seen for adults where weight gain tends to plateau over time.

Despite baseline differences in weight across the age groups and indications, overall there were no clear differences in patterns of weight gain between the patients with bipolar disorder and schizophrenia or the children and adolescents.

These findings are reflected in the U.S. label which contains a warning and a precaution regarding weight gain for both adults as well as children and adolescents, and recommends that weight gain in children and adolescents be assessed against what is expected for normal growth.

To review the vital sign conclusions, in short- and longer-term studies, we observed

increases in heart rate, as well as increases in mean blood pressure of up to 2 millimeters of mercury from baseline. These changes did not appear to progress over time. The etiology of the blood pressure findings is not fully elucidated at this time.

Increases in weight were seen in the short-term studies of approximately 1.6 kilograms, and 5 kilograms in the longer-term studies. Changes in BMI Z score seemed to plateau over longer-term quetiapine treatment.

Both blood pressure and weight can be monitored and managed. The data presented here have been included in the quetiapine label.

We will now change gears and discuss laboratory data, focusing on metabolic parameters, including lipids and glucose. It is important to highlight that changes in these parameters have been observed for medications in the atypical class, as previously mentioned today, and are included in the product labeling. We will also briefly discuss changes in prolactin in this part

of the presentation.

This slide summarizes mean changes from baseline for total cholesterol, fasting LDL, HDL and fasting triglycerides. Mean changes for placebo and quetiapine from baseline are presented. The mean changes for quetiapine are circled to help orient you to the slide.

In the short-term studies, the parameters with the greatest changes from baseline were total cholesterol, LDL and triglycerides, as you can see here. As presented in the briefing document, decreases in the LDL/HDL ratio were observed as 0.14 milligrams per deciliter.

The changes seen for children were similar to those of adolescents and can be found in the briefing document. There were no differences noted, when we examined the data, by indication or by dose.

This table shows mean changes in lipids for those that continued into study 150. The table is provided in a similar format as the weight data.

For patients previously treatment with quetiapine, decreases for all lipid parameters, including HDL, were seen from open-label baseline. For example, for total cholesterol, there were decreases in total cholesterol of 8 milligrams per deciliter for patients previously treated with quetiapine from their open-label baseline, with an overall change of 0.3 milligrams per deciliter from the double-blind baseline circled in yellow.

By contrast, for those patients previously treated with placebo, the magnitude of changes for cholesterol during open-label treatment, circled here in pink, were similar to the changes seen in the short-term studies that we reviewed on the previous slide. Patterns of change for LDL and triglycerides were similar.

As with weight, we also assessed with any patients had shifts in lipids. This is a simplified version of the data presented in table 14 of your briefing document. Patients who shifted across a threshold are presented for quetiapine and placebo. The thresholds selected

were based on the metabolic request the FDA made to sponsors of the atypical antipsychotic agents.

In short-term studies, shifts for quetiapine were greater than placebo for all the parameters except HDL. Most patients who had shifts to high values had borderline values for these parameters at baseline, with few patients shifting from a normal baseline to high values.

In study 150, additional shifts from the double-blind baseline were seen for quetiapine for all parameters and can be found in your briefing document. There were no discontinuations due to lipid abnormalities in short- or longer-term studies.

We will now move to a review of the glucose data. In contrast to most parameters presented today, differences by study were observed for glucose. You will note that baseline fasting plasma glucose levels were higher in study 112 compared to study 149. In study 112, approximately 62 percent of patients had previous antipsychotic exposure, compared to 26 percent in

study 149, which may account for this difference.

There are mean decreases in fasting plasma glucose seen in study 112 for quetiapine and placebo, with increases in fasting plasma glucose in study 149 seen for quetiapine only.

When examined by age within study 149, we can see that children had a greater mean increase in fasting plasma glucose compared with the adolescents at the end of the short-term studies.

In study 150, for the overall population, there were small additional changes from open-label baseline. In comparison to the short-term studies where we saw mean increases in glucose that were higher for the younger patients, in the longer-term studies, patients who continued on quetiapine that were children had decreases in their fasting plasma glucose levels, with overall changes in double-blind baseline very similar to those seen in adults and adolescents. There were no important differences by dose.

Shifts in fasting plasma glucose were examined as well, and in the short-term studies,

there were no patients who had shifts in fasting plasma glucose greater than 126 milligrams per deciliter. A total of five patients in the longer-term studies had shifts greater than 126 milligrams per deciliter. These five patients were examined in detail. For each of these cases, baseline abnormalities in glucose tolerance or risk factors for diabetes mellitus were observed.

The label for quetiapine does recommend that patients with diabetes mellitus or risk factors for diabetes mellitus be monitored for fasting plasma glucose.

This slide describes mean changes in prolactin in the individual short-term studies. This is a relevant lab primer to examine when treating patients with antipsychotics as these agents have the potential to block the dopamine D2 receptor, leading to increases in prolactin level, as is reported with the conventional antipsychotic medications.

The baseline prolactin values were higher in study 112 compared to study 149. As we

previously noted, previous antipsychotic use was higher in study 112 compared to study 149.

In study 112, there were mean decreases seen both for placebo and quetiapine, although the decreases were greater for placebo. In study 149, there was a decrease of approximately 1 nanogram per milliliter in prolactin for placebo and an increase for quetiapine of 2.3 nanograms per milliliter.

Additional decreases in prolactin were observed during study 150 of 0.9 nanograms per milliliter.

Shifts to potentially clinically high values were also reported for quetiapine more frequently than placebo and are provided in the briefing document. However, with few exceptions, all shifts were less than two times the upper limit of normal. There were also no clinical signs or symptoms of hyperprolactinemia reported for any patients in the pediatric program.

In adult studies, mean changes and shifts were similar for quetiapine compared with placebo

for prolactin. We did not see an increase in reported adverse events related to hyperprolactinemia for quetiapine compared to placebo in adult studies.

In conclusion, mean changes and shifts in lipids, glucose and prolactin were seen for quetiapine in the short- and longer-term studies. For nearly all patients, these changes did not lead to discontinuation from the studies. Because the pediatric data are limited, the long-term consequences of these findings is unknown. However, the changes in the laboratory parameters can be monitored and managed.

The final topic we will discuss today is ECG findings. In the clinical development program, centrally-read ECGs were obtained during the studies. Decreases in QTc Fridericia, or QTcF were seen both for quetiapine and placebo, with a quetiapine-placebo difference of 0.5 milliseconds. Importantly, there were no increases in QTcF greater than 60 milliseconds, or shifts greater than 500 milliseconds, nor were there any adverse

events of ventricular arrhythmias reported in the short- or longer-term pediatric studies.

Overall, these findings are consistent with the adult program where mean differences in QTcF for quetiapine versus placebo were minus 0.31 milliseconds.

Additionally, no events of Torsades de Pointes or ventricular fibrillation have been reported in over 26,000 patients treated in quetiapine clinical trials.

Overall, we have demonstrated today that the safety observation in pediatric patients ages 10 to 17 in studies up to 26 weeks are generally consistent with the known safety profile in adults, suggesting that children and adolescents are susceptible to the same risks for quetiapine as seen for adults.

The longer-term consequences of these risks have not been assessed in children and adolescents. Findings which appear to be unique for the pediatric patients include increases in supine blood pressure.

The safety data I've presented are important to understand as one considers quetiapine as a treatment option for children and adolescents with the serious psychiatric disorders of bipolar mania and schizophrenia. Importantly, these safety findings can be monitored and managed, and have been included in the U.S. prescribing information for quetiapine.

I will now turn the podium back over to Dr. Rak who will review the risk management program.

DR. RAK: Thank you, Dr. O'Dowd.

AstraZeneca's risk management plan includes risk assessment, risk minimization and education. It is important to note that the long-term consequences of the changes that we discuss today in children and adolescents are not known. Hence, these well-characterized and familiar short-term changes need to be followed closely in order to inform the individual benefit/risk conversation.

Risk assessment involves well-established

pharmacovigilance methods that monitor for new safety signals as well as changes in existing signals. We submit safety reports to the FDA in our periodic safety updates.

Our risk minimization activities begin with a label that accurately reflects benefit and risk. Final labeling will be made in accordance with FDA guidance.

In order to reinforce our risk management plan, several types of educational activities involving health care professionals, patients, caregivers and friends will be employed. These methods have already been used to communicate both benefits and risks for quetiapine in schizophrenia and bipolar disorder in adults.

Now I would like to welcome Dr. Lili Kopala to the podium to provide a clinician's perspective.

DR. KOPALA: I am Dr. Lili Kopala, and I'm a professor of psychiatry at the University of British Columbia in Vancouver. Much of my time is spent assessing and treating young people in an

early psychosis program. I'd like to share with you some of my clinical experience.

We know a great deal about Alzheimer's disease. It's in the news frequently. It's common. But it isn't until you put up the actual figures representing lifetime prevalence that you begin to see the effect that disorders that have their onset in early -- childhood/early adolescence that you can see how many individuals actually live with these conditions relative to the others.

On this slide are what we refer to as DALYs, or disability-adjusted life years. What you can see is that both bipolar disorder and schizophrenia are in the top ten conditions contributed to disability.

Now I will highlight a case of a young person I treated several years ago. We'll call him John, a 15-year-old student who came to the emergency room with his mother. She reported that John was talking to himself, hearing voices and responding to what the voices were telling him to

do. He appeared perplexed and confused and very distressed.

To put John's clinical picture in the PANSS rating scale that Dr. Eriksson and other have referred to, he would have a PANSS score of about 100, which means that he was markedly ill.

According to John, he had been hearing voices for at least three years, but didn't know it was illness. He was smoking cannabis nightly to try to get some sleep. John's mother sadly added that she didn't think she could keep going -- or John couldn't keep going with him in this condition. She had thought of suicide for herself and thought that even death would be preferable for John rather than continuing to live in his state. They were desperate for help.

John and his family were educated about psychosis and the effects of medication. They agreed that John would be treated with an atypical antipsychotic medication. He demonstrated, fortunately, a good response to treatment and had no side effects apart from sedation. And this

sedation lasted about a week. Both John and his mother were tremendously relieved.

After several weeks in hospital, he was discharged home and was able to resume school on a part-time basis. He engaged well with our early psychosis intervention team, and partook of many of the services offered. No further hospitalizations were required over the next two years.

John also regularly asked me when he could stop medication. I have to tell you, that's the most common question I am asked by young people, and older people too. It does provide an opportunity to discuss benefit/risk. What John demonstrates is how some families become desperate, not knowing what is going on with their teen. Once illness is explained to them and it comes together in some sort of sense that they can deal with, steps -- further steps can be taken.

Fortunately, John and his family were very open to taking medication, and they could see light at the end of a tunnel that was very bleak

at one point.

Schizophrenia and mania are considered to be complex disorders. So is diabetes. They're not caused by one environmental factor or one gene. And what this slide shows is that -- you'll see soon that there's an interaction between specific genes, the little blue balls, and environmental factors that actually contribute to the expression of illness.

An example of an environmental risk factor is bullying in young people in school. That's been talked about quite a bit these days in the news. And this comes out of a study that demonstrated that bullying increased the risk of preteens actually experiencing psychotic symptoms, and there was also a dose effect, interestingly enough; that is, the more episodes of bullying they had, the greater their risk was for expressing psychotic symptoms.

There are many examples of environmental factors. Immigration is one. Living in a city is another. Early childhood trauma, et cetera.

Cannabis use would also be considered an environmental factor.

For years I would attend meetings and there would be annual debates about the causes of schizophrenia and bipolar disorder, and there would be the geneticists on this side that it's all genetic, and over here people talking about environmental factors. And it hasn't been until more recently that this kind of debate has given way to an attempt to understand genes and environment interacting.

So it is genetic risk factors plus environmental risk factors that result in the expression of illness, what we call affected here in this slide. For example, in John's case, his use of cannabis may have aggravated his illness.

So what is going on in the brains of young people with schizophrenia and mania? And I ask this question knowing full well that there is a large cohort of people sitting on the panel who are very knowledgeable in this area.

While there are many things going on in

the brain -- and this is layered on brain development -- I'm going to focus on gray matter changes in schizophrenia, although there is some evidence for similar processes in bipolar disorder.

In a seminal study conducted at the National Institute of Mental Health by Judith Rapoport and her colleagues, many of whom -- some of these colleagues are in the room here -- children with early age onset schizophrenia, defined for us earlier, were followed up using MRI over five years. And what this slide shows is that there is evidence for loss of gray matter in both male and female patients, but not control subjects.

The color pink represents the areas of greatest gray matter loss, predominantly -- for people who aren't familiar with this area -- the top of the brain, or parietal regions, and then, somewhat later, frontal areas and here, the temporal areas.

This initiated a series of research

endeavors that demonstrated that schizophrenia is, for certain, a brain disorder, and the same can be said for bipolar disorder. These aren't conditions caused by poor parenting or poor schooling -- and, in fact, when I was a medical student, that's what I was taught.

More recently, there has been a study of adolescents and young adults with schizophrenia completed in Holland, and here's an overview of that study. van Haren and colleagues looked at 96 first episode patients with schizophrenia. This was a five-year study, and they had a very high retention rate, over 90 percent, which -- and I asked the lead authors whether there was something unique about Holland that would allow for such a high follow-up rate. Didn't get a response.

The majority were in the age category of 16 to 25. They were treated with either typical antipsychotic medications, clozapine or olanzapine. Most of those treated with typical antipsychotic medications were switched, over the course of this five years, to treatment with

atypical medications.

Here, circled in red, indicates the front of the brain here. And you can see that there was loss of tissue there -- this is baseline on the one side and then the five-year follow-up, and these are averages. And also you can see that the temporal lobes were affected, shown by the red arrow.

And so what does correlate with this gray matter loss? One of the main findings was that tissue loss is related to time spent psychotic, so being psychotic is not desirable. And you will remember that John described having psychotic symptoms for at least three years. And this is frequently the case. People just don't know what they're experiencing is illness.

The progression in frontal tissue loss is related to the number of psychotic relapses, and relapses are to be avoided. And that's one of the things, clinically, we spend a great deal of time doing as clinicians.

People who took atypical antipsychotic

medications had attenuated gray matter loss; that is, somewhat less gray matter loss.

Engaging patients in activities that we know to be beneficial, such as taking medications regularly, stress reduction and stopping the use of street drugs is something that our programs -- that people involved in our programs spend time on. For example, with John, stopping cannabis use could be targeted as one strategy to prevent relapse.

Given this data, how does this actually translate into what we do in the clinic? I've mentioned some of this already, but clearly symptom control is the top priority, both for the patient and the family, and sometimes the staff at the hospital. And that was very clear with John and his mother, as they were so desperate that they considered death.

One has to initiate dialogue and state that there were will be ongoing discussions about what to expect from treatment. Sedation is one side effect you've heard about frequently. It may

be desirable for some people, especially if they're not sleeping well at night, but it is not acceptable if one is trying to go back to school or return to a job.

Hypotension can be addressed by telling someone to be slow in getting up out of bed and to sit at the side of the bed until some light-headedness might pass. We certainly want to avoid EPS, extrapyramidal symptoms, as they are most uncomfortable for patients and akathisia has been reported to contribute to suicide. We want to avoid tardive dyskinesia, the longer-term sequela of extrapyramidal signs and symptoms.

With increased appetite and weight change, I usually tell my patients to keep track of what they're eating and write it down and bring it back to our next meeting.

One also needs to address potential longer-term side effects, including hyperglycemia, diabetes and possibly dyslipidemia.

Patients do need additional treatment options. I think that's been raised already.

They may respond to the first treatment you give them, but the side effects are unacceptable. And that indeed was the case for many years, when most of our medications were typical antipsychotic drugs, and everyone got EPS.

Not everyone has the same brain, clearly, not even in this room. Therefore, we shouldn't expect the same drug to treat everyone. A good example in medicine in hypertension because if you talk to a room full of people with hypertension, they will be on a variety of medications, some even on multiple medications. So it is very common to select medications that work and are acceptable to the person who is taking them.

In summary, my observations are consistent with those of the National Alliance for the Mentally Ill. Specifically, young people with serious psychiatric illness want to recover function. They want to go to school, have friends, get a job. In essence, they want a life.

Schizophrenia and mania are treatable. Quoting John, he would say, Get help early. He

thought that he was in a quagmire for far too long. He also added that medications work.

Not all patients are the same, so additional treatment options are needed. Thank you.

DR. RAK: Thank you very much, Dr. Kopala, for sharing with us your clinician's perspective.

The clinical data that we have reviewed today support a positive benefit/risk assessment in both serious psychiatric disorders for children and adolescents. Importantly, as Dr. Eriksson reviewed, efficacy was demonstrated in the pediatric program in the same conditions and with the same doses as in the adult studies.

The pediatric studies also used the same scales, and showed a similar magnitude of effect as the adult studies.

As Dr. O'Dowd reviewed, the potential risks of quetiapine treatment in pediatric patients are generally not different from those observed in adult patients with schizophrenia and

bipolar disorder for whom quetiapine is already approved. These potential risks are described in the current label for quetiapine.

Importantly, our experience indicates that the risks can be managed or minimized. We are committed to provide appropriate labeling for the treatment [sic] of quetiapine in these disorders in children and adolescents where more guidance may be appropriate for the treating physician.

We believe that the risks, including the ones we discussed today, are manageable in the context of informed patients and prescribers seeking to achieve the benefits of quetiapine treatment in these serious psychiatric disorders with few currently approved treatments.

As Dr. Vitiello and Dr. Kopala described, bipolar mania and schizophrenia in children are serious diseases with potentially devastating consequences. The evidence for benefit following treatment with quetiapine is compelling. Some risks are present, but these are well known and

can be managed. The benefit/risk is positive, and quetiapine offers a much-needed first-line treatment option. We are optimistic about the potential for quetiapine to help children and adolescents suffering with these disorders, and we look forward to the committee's discussions today. Thank you.

DR. GOODMAN: Okay. I want to thank AstraZeneca for a series of clear and concise presentations, for keeping us pretty much on time.

Now I'd like to open it up for questions by the panel, clarifying questions on the presentation. Dr. Pritchett.

DR. PRITCHETT: I have a question for Dr. O'Dowd. I think the heart rate change is a bit curious. I think you told us that -- we saw a little heart rate with the adults, and we accounted for that by saying there was some hypotension. But you don't have hypotension here, and yet you've got a heart rate increase that's, you know, 7 or 8 beats a minute compared with placebo.

Do we know what the mechanism is?

DR. RAK: So thank you for asking that question of Dr. O'Dowd, but I can answer, and then we can ask Dr. Philip Saul to help us. We do not have a mechanism. We do not understand these changes. This came as a surprise to us given that -- certainly quetiapine is associated with orthostatic hypotension. It was in the course of assessing changes for orthostatic hypotension using supine blood pressures that we came across this finding.

Because these are measures used as part of a orthostatic hypotension protocol, we focused on the supine blood pressures, thinking this would best approximate it.

So we have discussed mechanisms. I'll ask, if I may -- if the chair would recognize Dr. Philip Saul to come up and help address this.

DR. SAUL: Thank you. I had found that curious as well. And one of the first questions I asked was, could there be a muscarinic blocking effect of this drug? And I'll review some of that

data. And then the other question was, are there norepinephrine effects?

And it turns out that the only pharmacokinetic difference that turned up in the difference between adults and adolescents in their study was that the norquetiapine levels were actually higher in the adolescents than in the adults, and they were even higher in the younger -- in the children, in the 10- to 12-year-old age group.

If you look at the in-vitro effects of norquetiapine, which is one of the main metabolites on -- in fact, if I can put this slide up that's here. Thank you.

If you look at the effects on this slide, it turns out that the -- that if we look at the M1 receptor right here -- and norquetiapine are the gray bars and quetiapine is the white bar, you can see that -- I'm sorry. I've got that reversed there. Yes -- no, that's correct. That the effect of norquetiapine on the M1 receptor, on the muscarinic 1 receptor is greater.

And then if we look at the norepinephrine transport mechanism here, you can see that the same thing is true for the norquetiapine there.

So both of those mechanisms could contribute to a larger change in heart rate and a larger change in blood pressure: The muscarinic blockade by making heart rate higher, with a subsequent effect on blood pressure through increases in cardiac output; and the norepinephrine transport through build-up of norepinephrine in both the cardiac and peripheral sympathetic receptors.

And that was the only explanation I could come up with that seemed to fit the data pretty well.

DR. GOODMAN: Assuming, for a moment, that those are the mechanisms that explain it, do you have any safety concerns?

DR. SAUL: I'd say -- as a cardiologist, my primary safety concern would be for the shifts in blood pressure, rather than -- I mean, if you think about it from a pediatric perspective, a 2

millimeter change in blood pressure doesn't mean anything in an individual. It's really the shifts that matter, whether you get into the hypertensive range.

And certainly those would be long-term safety concerns in an individual which could be managed in a variety of different ways. One would, of course, be to manage the blood pressure because the psychiatric condition is serious enough that the drug is working and you want to stick with it. And the other would be to change drug -- psychiatric drug therapies, and to me that would be an individual decision.

If I were sent that patient as a cardiologist and asked what to do, I would leave it up to the psychiatrist and say, I'm happy to manage the blood pressure if you'd like or, if you want to switch therapies, I'm happy to recheck the blood pressure.

DR. GOODMAN: Dr. Pritchett, any follow-up?

DR. PRITCHETT: Well, I think -- if this

were an adult in the coronary prone age group -- or a patient with heart failure or known coronary disease, you'd be worried about a drug that increased the heart rate 8 beats a minute. In children, it's probably not a big deal. You know, I think -- you know, there was an excess of tachycardia reported -- you know, there are -- a lot of things lead into a MedDRA diagnosis of tachycardia. I mean, who knows was going on there? But that's sort of what you would expect with a drug that does this.

But I think, functionally, you know, this heart rate change wouldn't be much of a problem for a child -- adolescent. So I'm -- I'm not worried in this age group.

DR. GOODMAN: Dr. Granger, you have your finger on the button.

DR. GRANGER: Yes. I also -- I share these kind of concerns about this observation, and I also probably was more concerned --

DR. GOODMAN: A little closer to the mic, please.

DR. GRANGER: I was also more concerned about the blood pressure increase, per se, than the heart rate increase where there was this substantial increase in people who had -- you know, I think a clinically meaningful increase in systolic and diastolic blood pressure.

So -- again, I'm not as familiar exactly what that means in the pediatric population other than it can't be a good thing, and I think it does need to be -- you know, it already is in the label. I think it certainly needs to be highlighted as something -- again, especially in these younger people.

I guess the other question is, in the very young, if this is the mechanism, this metabolite having these effects, you know should there be consideration for lower -- was there a dose effect in the younger age group related to this effect on blood pressure and heart rate?

DR. SAUL: There didn't seem to be a dose effect either in the --

DR. RAK: We should get somebody else

to -- thank you, Dr. Saul. Let's have Dr. Liza O'Dowd come back and review our data with us again and specifically answer that question.

DR. O'DOWD: From study 28, which is our PK study, we did have PK data collected at a variety of time points, and of course we also had the blood pressure collected at various time points.

This slide will show you dose versus blood pressure, and we did not see any evidence, obviously, of a dose response over the ranges tested. And if we extended that out to the 800 milligrams, it would be similar.

What I can tell you is that when we looked at metabolites, norquetiapine and quetiapine levels in the plasma, what we saw was that, for heart rate, there was a little bit of a relationship between concentration of quetiapine and norquetiapine in heart rate. However, we did not see a relationship between those concentration and blood pressure changes in study 28.

DR. GOODMAN: Any further comment on this

particular issue on tachycardia? Dr. Woolson?

DR. WOOLSON: I had a question about some of secondary outcome measures --

DR. GOODMAN: Let me go back and -- we've got a couple of people ahead of you, so I'll put you on the list.

Dr. Cnann?

DR. CNANN: I had a question about the dosing study 149. Study 28, the PK study, had doses 400 and 800, but 149 used 600. Can you clarify the rationale why 600 was used?

DR. RAK: I'll ask Dr. Eriksson to address that question.

DR. ERIKSSON: As I mentioned previously, we had substantial input from practicing children and adolescents psychiatrists, and we also had information from a clinical trial that had been conducted. It really appeared as if 400 and 600 milligrams would be sufficient doses to achieve clinical efficacy. So that was the reason. We didn't really see the reason to go beyond 600 milligrams for this study in mania.

DR. GOODMAN: Do you want to follow up to that or are you satisfied with --

DR. CNANN: Well, in general, I think we haven't seen very much dose response in any of these studies, and it would be a question of interpretation, what we do with that.

DR. RAK: If I may address that question, yes, it's correct that these studies were not designed to look for a dose response relationship. We did studies looking for dose response relationships in the adult program. Even in the adult program, dose response in the psychiatric disorders are difficult to establish.

We felt that the doses selected for this program were appropriate per the rationale that Dr. Eriksson described. And if the Chair would permit us to recognize Bob Kowatch, who is an expert in pediatric mania, to address specifically the question the utility of those doses versus higher doses or lower doses.

DR. GOODMAN: Sure. Go ahead. Thank you.

DR. KOWATCH: I'm Robert Kowatch. I'm a child and adolescent psychiatrist. I'm affiliated with the University of Cincinnati. We have tried lower dosages in patients clinically, and we don't get a response. We typically, you know, will start at 100, 200 milligrams on inpatients. We found the sweet spot to be about 400 to 600 milligrams per day.

So we've not clinically found doses to be effective.

DR. GOODMAN: Okay. Thank you.

Dr. Grady?

DR. GRADY-WELIKY: I had a question regarding an item in the briefing document that mentioned there were some abnormalities in the slit-lamp examination of some of the patients, and I was wondering if you could comment on that, if there's any more follow-up on that.

DR. RAK: Okay. I'll ask Dr. Liza O'Dowd if she could please come up and address that.

DR. O'DOWD: There are three patients who had abnormalities in their slit-lamp exam in study 150, the open-label study. And one of these

was believed to be congenital findings, on examination by the ophthalmologist. The second was a case of some sub-capsular changes which were described as not visually impairing. And the third was an abnormality that was found after only about ten days of therapy, so it was felt by the ophthalmologist not to be related to quetiapine.

I think it might be useful if I gave you some additional information around the cataractogenic potential of quetiapine. We've had a long ongoing study looking at cataracts for quetiapine, and I could share with you results that have just become available really in the last month or so.

The study was called the CLEAR study, and what it did was looked at the cataractogenic potential of quetiapine. We used risperidone as a comparator because risperidone is believed to be a drug that doesn't have the potential to develop cataracts.

And what I can share with you is that

quantitatively and qualitatively, the differences for quetiapine were lower than seen with risperidone -- not to say that risperidone caused an increase in cataracts, but rather we did not see more events for quetiapine compared to risperidone.

So, taken together, we don't find, for quetiapine, that the drug appears to have a cataractogenic potential based on this. And this data hasn't been shared with the FDA. We just have gotten it, but it will be provided to them in due course.

DR. GOODMAN: Dr. Day?

DR. DAY: Yes, I had a question about the same information in the briefing document, and thank you for the update. I was wondering how you decide when to present categorical results only versus a more continuous measure, so there are only these two or three people whom you've noted shifted to the abnormal category, but there could have been slight shifts across everybody, just depending upon where they started at baseline.

So is there a general policy about when to present categorical only versus continuous data? Or is it something specific to looking for cataracts?

DR. RAK: So I'll start, and then I'll ask Kurt Engleman, our statistical expert, to come up, if he has anything to add. But there is no policy in terms of how we analyze or present the data. As I'm sure you all recognize, we have lots and lots of data. We look at it in every conceivable possible way. Our goal is to characterize the data accurately and then work with internal and external experts to interpret it.

DR. GOODMAN: Dr. Vitiello?

DR. VITIELLO: I was wondering if you had any data about drug discontinuation, meaning would a clinician expect to see any withdrawal symptoms? Are there any recommendation when the drug needs to be discontinued? If you have an adolescent with 800 milligrams, would you recommend to taper the drug gradually -- or if you have looked into

this.

DR. RAK: Yes, we have looked into this in the adult program, and we've looked at the benefits of a more gradual discontinuation of higher doses and, yes, in fact, there is benefit in more gradually discontinuing patients at the higher doses.

With regards to specific data in the pediatric program, we don't have any of that data with us, no.

DR. GOODMAN: Ms. Lawrence?

MS. LAWRENCE: Thank you all. I really appreciated Dr. Kopala's view on her patient. And I guess I would like either a cardiologist from our own committee or somebody from AstraZeneca to give an opinion on the long-term use when a child age 10 or 14 starts with this drug -- the long-term effect of the increased heart rate into adulthood.

DR. RAK: I'd ask the Chair who you'd prefer I --

DR. GOODMAN: Well, we'll hear from both.

DR. PRITCHETT: I think the answer is we don't know, although the heart rate effect that was seen in children was not seen in adults. So maybe if you happen to have a child who took this for decades and became an adult, maybe it resolves when they reach adulthood. I mean, we don't know.

I guess I'm wondering, for all of these compounds, how long does a patient actually take them? I mean, do people really take them for years or do they -- they take them for a while and then they have side effects or they don't work and we reach into the toolbox and pull out something else, so we're really not exposing somebody for decades to this heart rate increase --

DR. GOODMAN: No, we might be, but I'll let others comment on that. Dr. Towbin, maybe you want to answer that.

DR. TOWBIN: Indeed, I think that we are looking at individuals who may have years-long treatment with this.

DR. RAK: And if I just may clarify for the record, the heart rate changes that were seen

in children are comparable to changes in heart rate that we've seen in adults. It's the blood pressure changes that we found in children are different from adults. So just to clarify.

MS. LAWRENCE: Can I go back and interrupt a second with our own advisory committee? Aside from antipsychotic, typical, atypical drugs, if you're treating a child who has some condition with an abnormal heart rate, long-term use of a medication, does that -- I guess it could hopefully benefit if someone goes into an adulthood with being on a medication for a long time.

DR. GOODMAN: Dr. Granger?

DR. GRANGER: I'll come back to the blood pressure because I think more important than the heart rate is the blood pressure. And a 20 millimeter increase in systolic blood pressure over a lifetime would be almost certainly a highly substantial increased risk later in life of fatal and disabling cardiovascular conditions.

So I think that's why, for that -- that's

why I think -- this is a very important issue, and at least monitoring and management -- and I share these concerns about -- you know, we have a three- and a six-week randomized data, we have six months of data without a comparator to really have any confidence in the comparison of safety issues. And then we have drugs that are used for years.

So that's part of the challenge, isn't it? It really is a lack of sufficient duration of treatment to have a better idea about what the impact of these safety issues might be.

DR. GOODMAN: We're going to let AstraZeneca respond.

DR. RAK: Yes. I was going to ask Dr. Lili Kopala to come up and give a clinician's perspective on how this would be managed, if the Chair feels that the cardiology aspects have been --

DR. GOODMAN: No. I think we have some other questions. Let's consider with some --

DR. RAK: Well, should I have Dr. Saul come up or have you go to another question?

DR. GOODMAN: Let's go to another question because I think it's an important discussion. We'll be returning to it both today and tomorrow.

Dr. Woolson, thank you for being so patient.

DR. WOOLSON: No problem. Of course any time you have withdrawals in a study, that's a problem, and we have to worry about it in the statistical analysis. And to a certain extent, with the primary outcome, that's been taken care of with the mixed model that has been used for the analysis.

But for the secondary outcomes -- and here is where I have -- I think these are helpful outcomes, but it wasn't clear to me how the withdrawals were handled in the secondary assessments, and I wonder if you could clarify that for us.

DR. RAK: Sure. If we could please put up the core slide for the secondary outcomes. Should we go first to the mania study and then

we'll go to the schizophrenia study?

You'll see -- under the list of the secondary outcomes you'll see mention of analyses, whether they were MMRMs or LOCFs. So -- I'll wait for that slide to come up.

So this is the core slide that lists the secondary end points. So this is the first study that was discussed.

DR. WOOLSON: I was particularly interested in the one secondary outcome that dealt with the proportion of individuals who had the 50 percent response in the mania scale and then 30 percent reduction in the schizophrenia. I thought that was a particularly important secondary outcome.

DR. RAK: Yes. So this is the first study, the mania study, that showed the response rates that were analyzed using the LOCF, and both you can see were statistically significant at a 50 percent reduction to determine a response rate.

Should we address this first or look at the next slide and then address them together?

DR. WOOLSON: So just -- to raise just a question here, you could have taken the individuals who withdrew early for a particular bad reason -- you could have just classified them as not having had a favorable response. I was wondering why that wasn't done.

DR. RAK: Okay. I'll ask Kurt Engleman, our statistical expert, to come up and address that, and then we'll be ready to move to study 112.

DR. ENGLEMAN: Good morning. Kurt Engleman, AstraZeneca biostatistics. In this analysis, that's actually what was done. If somebody withdrew early for any cause, they were -- they were classified as having a response or remission based on their observation at the final time point.

In reality, very few patients that were actually responders or remissions withdrew early.

DR. RAK: The next is study 112 where you'll note that the secondary outcomes response rate, which here was defined as 30 percent or

greater -- in Dr. Vitiello's presentation of TEOSS, I believe the responder rate was 20 percent or greater, but these response rates, although not statistically significant, are in the range -- here it is -- in the range of the findings, I believe, in the olanzapine treatment arm.

And here you can see LOCF was also used.

Kurt, anything to add? No?

DR. GOODMAN: Is that clear to you now, Dr. Woolson? Okay.

Dr. Gogtay?

DR. GOGTAY: I have a couple of questions that are not necessarily related to each other. The first one is, was Seroquel given always in a single-day dosing or divided doses?

DR. RAK: In this program, Seroquel was administered either twice a day or three times a day.

DR. GOGTAY: And that was decided based on the clinical response, or the clinical management requirements?

DR. RAK: I'll ask Dr. Eriksson to come

up and say how exactly that was decided.

DR. ERIKSSON: At the time these studies were initiated, there were somewhat differing practices among clinicians. Some used two times daily, some used three times daily.

So what we did in this study was that we recommended clinicians to start with two times daily, but there was a possibility to go over to three times daily if warranted. But only about 15 percent of the patients received three times daily.

And we can also see, in the longer-term study, that the proportion of patients with three times daily went down.

DR. GOGTAY: And then do the outcomes -- or the side effects, particularly, do they vary depending on the dosage regimen?

DR. ERIKSSON: Generally I think we can say that we have seen -- for tolerability -- maybe you'll take that.

DR. RAK: Yes. We did look at that, and we've shared that analysis with the FDA. I know

they're reviewing it also. It is an important question.

Dr. O'Dowd.

DR. O'DOWD: There was -- again, as Dr. Eriksson mentioned, only about 15 or 16 percent of patients received TID dosing. So the numbers are small. Generally the AE profile was broadly similar. There was a little bit of a higher incidence of dizziness, appetite, dry mouth, tachycardia and somnolence with a TID dosing versus the BID dosing. But, again, the numbers are -- the sample sizes are much smaller, so you take that with a bit of -- grain of salt. But that's the pattern that we saw.

DR. GOGTAY: In terms of the weight gain data, do you have any idea about how does it compare with the weight gain seen in adults?

DR. RAK: Yes. I'll ask Dr. O'Dowd to come up and give us that comparison.

DR. O'DOWD: One thing you must consider is adults should not be growing, so we have to take that into context. So, numerically, there's

more pounds per weight gain that happens in the children over the long term, but again, we have to take into consideration that they're growing.

This data that I'm going to show you is from an analysis we did as part of the FDA metabolic request. And what you'll see in the top is a lot of numbers that represent doses of quetiapine from 50 milligrams per day to 800 milligrams per day.

And what you can see is the baseline weights, which are obviously much different in adults than children, and the changes in weights. And I'll focus your attention on the right-hand side of the screen where you see doses of 400 to 800 milligrams per day. And in short-term studies of four to eight weeks' duration, we see about 1.1 to 1.4 kilograms of weight gain. For children we see changes about 1.5 to 1.7 kilos per [sic] weight gain in similar time frames.

DR. GOGTAY: A couple more questions. One is, is there a head-to-head comparison between Seroquel and mood stabilizers in bipolar I illness

in children?

DR. RAK: We do not have that study, but I believe there may be a study in the literature that adds quetiapine to valproate versus valproate to -- and placebo. So I don't know -- Dr. Christoph Correll, would you come up and address that question, please. But we do not have that study as part of our program.

DR. CORRELL: Christoph Correll, Zucker Hillside Hospital and Albert Einstein College of Medicine. I'm a child and general psychiatrist.

There are two studies in the literature that were both published by Melissa DelBello. One is the one that was just mentioned where quetiapine was added to valproic acid and compared to just valproic acid alone. And the other one was a head-to-head comparison. Both are pretty small studies, about 50 patients or less.

Do you have any questions about outcome or weight gain or --

DR. GOGTAY: Yeah. Is there any general comment about the outcome? Does quetiapine have

any benefits over --

DR. CORRELL: So for the add-on study, like in adults, combining an atypical antipsychotic -- in this case, quetiapine -- to a mood stabilizer fared better than just the mood stabilizer alone.

Numerically, there was a little bit more weight gain and sedation, but that wasn't statistically significant, and efficacy was not related to sedation.

In the head-to-head study itself, there was no statistically significant difference in the primary outcome, but it appeared that more patients on quetiapine had much -- very much improvement or also reached remission.

DR. GOODMAN: We have several more people that have questions, and we're running a little behind here. I'll try not to encroach upon Phil Chappell's time either. So we'll make up for it sometime later.

Dr. Temple?

DR. TEMPLE: This is for Dr. Eriksson.

It's about the primary end point, and particularly slide 23. It's described as an MMRM analysis in the ITT population, but it has a very small number of patients. The number of patients in the analysis is only the completers. So -- I always thought the MMRM analysis was an improvement over LOCF so you could actually take all patients into account. But this appears to have only the patients who completed it.

Can you clarify that?

DR. RAK: I think Dr. Eriksson would prefer our statistical expert answer that --

DR. TEMPLE: That's fine.

DR. RAK: Kurt Engleman.

DR. TEMPLE: Our reviews have similar analyses, so this isn't unique. And this isn't calling the overall effectiveness into question. There's many secondary analyses. But I was just curious about what the primary analysis was.

DR. ENGLEMAN: Yes. The slide -- the analysis method does take all of the patients into account. What you have are the patients that made

it to that specific point as a reference. So...

DR. TEMPLE: The slide says -- it gives numbers -- sample sizes of 54, 55 and 43. That's only about two-thirds of the patients in the study.

DR. ENGLEMAN: Those are the patients in the study at day 42. The analysis itself does incorporate all the patients in the analysis.

DR. TEMPLE: So isn't that a sort of curious presentation?

DR. ENGLEMAN: Well, I guess -- I apologize for the confusion.

DR. TEMPLE: Okay. But it really does account for all the patients. It's the improved modeled version of LOCF?

DR. RAK: It appears this may need a footnote --

DR. TEMPLE: Yeah.

DR. RAK: The slide. Thank you.

DR. GOODMAN: Dr. Caplan?

DR. CAPLAN: My question is, are the patients who developed the vital sign side effects

the same ones as those who also developed the metabolic side effects? Or how many of them were in common?

DR. RAK: So I'll ask Dr. Liza O'Dowd to come up and address that.

DR. O'DOWD: There were not that many actually in common. What we did is we looked at patients who had changes in weight and compared it to changes in blood pressure and lipids. I would say the most common finding might be changes in weight. About 20 percent of the children that showed some blood pressure [sic] had changes in weight, defined at a 7 percent increase.

There were very few patients who had changes in blood pressure associated with a constellation of weight or lipid abnormalities.

DR. CAPLAN: And I have another question, and that is in terms of the information on sui, was that a specific question that was asked as part of the study, or that was sort of retrospectively collected using the Columbia approach?

DR. O'DOWD: The Columbia analysis was done by the investigator, and it was analyzed retrospectively.

DR. CAPLAN: What you're saying is it wasn't a specific question asked of every subject.

DR. O'DOWD: The subjects were not asked if they were having suicide thoughts, no.

DR. GOODMAN: Dr. Towbin?

DR. TOWBIN: Yes. I just had a couple of questions about study 149. The first question relates to the inclusion criteria. And I not that, of course, it was permissible to have a diagnosis of attention deficit hyperactivity disorder. This is very common comorbidity for bipolar disorder in children and youth.

But I'm curious about how you handled individuals who had overlapping symptoms of distractibility, agitation of hyperactivity when you were including them in the study -- that is, individuals who had a background of chronic symptoms of that kind -- as you were rating them for the presence of bipolar disorder.

DR. RAK: So I believe the guidance was very clear to the investigators that it had to be primarily a diagnosis of bipolar mania in children. It could not be the primary diagnosis. We relied on the judgment of the investigator.

I could ask Dr. Eriksson to comment more on the instructions that we gave, or ask Dr. Kowatch to comment on how realistic is it that that can be done precisely.

DR. TOWBIN: I do believe it can be done precisely if one is asking about whether there is an increase in those symptoms that goes along with the episode, if you will, of bipolar disorder, as opposed to this background chronic problem that might then overlap with irritability.

DR. GOODMAN: So do have anything to add to that, Dr. Eriksson?

DR. ERIKSSON: In this program, we included patients who had mania. We were not seeking out patients with mixed episodes. So in that respect, the population is a bit more homogenous.

Also, when we analyzed outcome, we see no difference in -- in outcome between the patients who had ADHD and who had no ADHD, as well as the patients who were on psychostimulants and not.

DR. TOWBIN: Well, actually, that gets to my second question; that is, what was the rationale for continuing stimulants in this population that you thought had acute mania? Most clinicians, seeing an individual with mania on a sympathomimetic drug would discontinue it, and so I was curious about what led you to make that decision?

DR. ERIKSSON: We had several patients, as I mentioned, on ADHD in this program, about 45 percent, but most of these patients were not on psychostimulants. But we did not instruct the investigators to discontinue ongoing psychostimulant use.

DR. TOWBIN: Can you tell me the rationale for that?

DR. ERIKSSON: We did recognize that there is a comorbidity between these two

disorders, and we did not want to actively intervene in the ongoing treatment for what we believed to be a bona fide concomitant ADHD, and also the ongoing psychostimulant use was only allowed if it had been ongoing with the same dose for 30 days.

DR. TOWBIN: I understand. It's just that if one saw a deterioration in a patient's functioning on an agent that was likely to be contributing to that problem, it seems only rational that one would discontinue it.

DR. ERIKSSON: The investigator was not forbidden to discontinue treatment.

DR. GOODMAN: I'm going to give Dr. Granger the opportunity to ask the last question before the break.

For those of you who still have questions, save them up for later. There will be other opportunities.

DR. GRANGER: The concern over sui has been mentioned as a key reason for having new drugs available. And yet is seems as though, even

though not statistically significant, this five versus zero in suicidal thought/ideation, seems to be concerning and consistent with some of the other concerns in this population.

Do you have any other data to reassure that that might be a transient effect? Or how do we put that into context with respect to the safety of this drug?

DR. RAK: Yeah. We don't have data that would be more reassuring. However, I will ask Dr. Lili Kopala if she could address that, and then if Dr. Christoph Correll has anything to add. Because it is a very, very important question, and our data set is limited.

DR. KOPALA: Well, I think we rather forget that we are dealing with very serious conditions, and people do think of suicide, reflect on it, think, is what my life is going to be? Or are tormented by hallucinations or have delusions.

So -- these symptoms don't necessarily go away overnight. So I don't know so much whether

you could say a drug effect or whether people are still on their recovery curve and still have thoughts of self-harm.

DR. GRANGER: But the data you showed had five events on drug on zero on placebo.

DR. KOPALA: Yeah. I can't account for that distribution. It may be random.

DR. GRANGER: It's not statistical, but it makes you wonder.

DR. RAK: We'll ask Dr. Liza O'Dowd if she can comment in greater detail on the cases that we had.

DR. O'DOWD: This slide breaks down the patients who had suicide ideation or attempts, including the cases that were -- had insufficient information to be clear about the intent. And I think it's important that we look at these in a little bit more detail because it is important to understand these patients in more detail.

The first thing to observe is, on the far left, you can see the five events resolved while the patients continued on quetiapine. Their

ideation, et cetera, improved as the children continued on drug therapy. That provides a little bit a context.

One child was involved in a motorcycle accident. There was no details around whether or not the motorcycle accident -- why it happened, so it was included in the Columbia analysis.

There's a child who had a malignancy and was discharged from the study because he was diagnosed with a malignancy, and was put on quetiapine by the prescribing physician after he was discharged from the study, and the ideation he had for suicide resolved.

One patient was not taking their study medication at the time that they -- actually, was non-compliant with study medication at the time of the event.

And two patients were discontinued from the study. One was -- had -- the last information we had was that they still were having suicidal thoughts, even after discontinuation.

So these are important events, and we

need to understand what's going on with these children. I thought it would be useful to provide a little bit more context around the details of the cases so you had a more full understanding of them.

DR. GOODMAN: Dr. Laughren?

DR. LAUGHREN: I agree that it's difficult to make sense of these few cases, and also given the individual circumstances of the cases. It's important to point out that quetiapine has a boxed warning for suicidality. Not because -- it's not based on any particular data. It's based on the fact that it's been shown to have antidepressant effects, and as all antidepressants, it has been tagged with that box. So -- it's not as if clinicians are not alerted to the possibility.

DR. GOODMAN: We're going to take a ten-minute break. Let me just remind panel members not to discuss the issues at hand, including among each other.

(A recess was taken.)

DR. GOODMAN: Okay. Is everybody present and accounted for? Dr. Rak from AstraZeneca had a slide he wanted to show -- wanted to make a correction.

DR. RAK: Thank you for the opportunity to correct the public record. In response to a question on the blood pressure changes seen during the pharmacokinetic study, Dr. Liza O'Dowd showed this slide -- and I'll ask her to come up and correct what this slide actually shows.

DR. O'DOWD: Actually, it shows what it's supposed to, supine standing blood pressure by dose. Someone with sharper eyes than we did caught that the Y axis is mislabeled. It does indeed represent supine blood pressure. I can assure you that, for the slide that shows diastolic blood pressure, the findings look very much the same. So again, there is no change in systolic or diastolic blood pressure by dose.

So apologies for that need for clarification.

DR. RAK: Thank you.

DR. GOODMAN: Okay. Thank you.

Our next presentation will be by Dr. Phil Chappell of Pfizer, Incorporated.

DR. CHAPPELL: Good morning. My name is Phil Chappell. I am the clinical lead for the Pfizer pediatric development programs, and I am also by training a child and adolescent psychiatrist.

This morning I will be reviewing with you the results of our pediatric bipolar development program and going over data we believe demonstrate that ziprasidone is both generally well-tolerated and efficacious in the treatment of children and adolescents with bipolar 1 disorder.

Ziprasidone is approved in adults for the treatment of schizophrenia and bipolar disorder, and the pediatric studies I will be presenting today were conducted to address the requirements of the Pediatric Research Equity Act and to fulfil the bipolar part of a written request that we conduct studies in children and adolescents with bipolar disorder.

In the written request, the FDA agreed that a single, well-controlled study would be sufficient to support a pediatric label, and also agreed that we did not need to study children below the age of ten years.

According to guidelines published by the American Academy of Child and Adolescent Psychiatry, bipolar 1 disorder bipolar 1 disorder can be reliably diagnosed in children age 10 to 17 using the adult DSM-IV criteria for bipolar disorder.

As we heard from Dr. Vitiello and other speakers this morning, pediatric bipolar disorder can be more severe and more chronic than adult bipolar disorder. These children have low recovery rates, frequent relapses and long mood episodes, and about half have an inadequate response to currently available treatment. Recently publications have also shown us that up to 80 percent of youth with bipolar disorder will grow up to be adults -- young adults with bipolar disorder. Weight gain is also a serious concern,

as up to 42 percent of children with bipolar disorder are either overweight or obese.

Now, before talking about our clinical studies, I would like to say a few words about the pharmacokinetics of ziprasidone in pediatric subjects. Comparison of PK data from pediatric and adult subjects has shown that the principal patient characteristic determining exposure is body weight. As body weight increases, clearance increases. Age has only a modest effect on exposure to ziprasidone.

After we correct for body weight differences, we can attain similar exposures to ziprasidone in children, adolescents and adults. Therefore, a weight-based dosing regimen was adopted for use in our pivotal bipolar study.

Our pediatric bipolar disorder program consisted of three key studies. Shown on the top left of the screen, study A1281123 was an open-label fixed-dose titration study that we conducted first to determine the most appropriate weight-based dosing regimen to use in our pivotal

trial. This study consisted of two periods. The initial period was a three-week fixed-dose titration that explored different weight-based dosing regimens. And period 1 was followed by a 27-week open-label flexible-dose safety extension study which contributed to our long-term safety database.

Shown on the right side of the screen, study A1281132 was a pivotal four-week double-blind placebo-controlled study. This study provided the controlled short-term efficacy and safety data which formed the basis of this submission.

Shown on the bottom of the screen, study A1281133 was a 26-week, open-label flexible-dose extension study of study A1281132 which also contributed to our long-term safety database.

The design of our pivotal four-week safety and efficacy trial consisted of an initial run-in period from one to ten days, during which subjects were washed out or disallowed

medications. This was followed by four weeks of double-blind treatment with weekly study visits.

At the end of the four-week treatment period, or at early termination, patients were eligible to be rolled over into study A1281133, the open-label extension study, if clinically indicated.

Subject were randomized at baseline to either ziprasidone or placebo in a 2-to-1 ratio. Weight-based dosing regimens were used whereby the target dose for subjects weighing 45 kilograms or greater was 120 to 160 milligrams a day and the target dose for subjects who weighed less than 45 kilograms was 60 to 80 milligrams a day.

In every case, the initial starting dose was a 20-milligram capsule of ziprasidone which was given at bedtime on the evening of the day the subject was randomized. Thereafter, the dose was flexibly titrated over the next two weeks up to the target dose.

Generally, the dose was increased by a 20-milligram capsule every couple of days until

the target dose was reached, although faster or slower titration was permitted based on clinical judgment.

The key inclusion and exclusion criteria for our study were that subjects had to be between 10 and 17 years of age and had to meet the DSM-IV diagnostic criteria for bipolar disorder. The diagnosis was based on a clinical interview by a child psychiatrist, and confirmed by the K-SADS semistructured diagnostic interview.

Current symptoms had to have been present for at least seven days prior to screening, and subjects were also required to have a total Young Mania Rating Scale score of 17 -- at least 17 at screening and at baseline.

Subjects with a significant cardiovascular history, including conduction abnormalities, history of arrhythmias, or a QT prolongation, or who had an abnormal ECG at screening or baseline were excluded from the study. We also excluded subjects with mental retardation, autism or pervasive developmental

disorder, as well as any subject who was doing well on an established and stable treatment regimen.

The primary efficacy variable in study 1132 was the change from baseline at week 4 in the YMRS total score. An important secondary efficacy variable was the change from baseline at week 4 in the Clinical Global Impression of severity score. We also obtained additional secondary efficacy end points as well as exploratory outcome end points, including the clinical -- the Children's Global Assessment Scale.

In addition to the usual safety assessments, the safety assessments included fasting metabolic laboratories, measurement of BMI and calculation of the BMI Z score, Tanner stage self-assessments and measurement of hormones involved in sexual maturation and growth. We selected the BMI Z score to evaluate changes in body weight because, as you have heard, it takes into account expected growth in height and is

based on age and sex-adjusted norms.

Special safety assessments included movement disorder rating scales, assessment of suicidality and a neuro-cognitive battery. Suicidality was systematically assessed at screening with the Suicide and Self-harm Questionnaire. Subjects were also monitored during the course of the study at every visit for emergent suicidality, using the suicide item from the Children's Depression Rating Scale - Revised, as well as a clinical interview.

In addition, the adverse event database was periodically reviewed during the course of the study to identify any potentially suicide-related adverse events. These events were then submitted to our data safety monitoring board and thereafter submitted to experts at Columbia University, so the data were classified according to the Columbia Suicidality Classification system.

This study was designed to have 85 percent power to detect a true difference between drug and placebo equal to the median treatment

difference in the change from baseline of the YMRS total score we observed in our adult ziprasidone mania trials. Alpha was set at 5 percent two-sided. Under these assumptions, the sample size estimation required that 222 subjects be enrolled in a 2-to-1 ratio, with 148 being randomized to ziprasidone and 74 to placebo.

A total of 327 subjects were screened and 238 were randomized. One randomized subject dropped out of the study before receiving the study drug. Therefore, 149 subjects were treated with ziprasidone and 88 with placebo.

As shown, 65 percent of the ziprasidone and 58 percent of the placebo subjects completed the trial. A similar proportion of subjects dropped out of each treatment group due to adverse events, but fewer ziprasidone-treated subjects discontinued due to lack of efficacy compared to the placebo group.

The two treatment groups were comparable in terms of demographic characteristics The placebo group had a somewhat higher proportion of

subjects in the younger age category, but this difference was not statistically significant.

The baseline clinical characteristics of the two groups were also generally comparable, with the exception of a higher level of psychotic symptoms in the placebo group.

The most recent mood episode in both treatment groups in the majority of subjects was a mixed episode. And the mean duration of the current episode in both groups was five to six months. The majority of the subjects in the study had previously been treated with psychotropic medications.

Here we see the baseline clinical severity ratings. They were comparable across the two groups. Taken together, they indicate a moderate to severe level of psychopathology. And as you can note from these mean C-GAS scores and the percent of subjects with C-GAS scores in the normal functioning range, this was a seriously impaired group of youngsters. Also of note, more than 40 percent of the subjects had a parent -- at

least one parent who had bipolar disorder. 60 percent of the subjects -- more than 60 percent of the subjects had an extended family history of bipolar disorder.

In terms of comorbidities commonly seen in children with pediatric bipolar disorder, 40 to 45 percent of our subjects had a comorbid diagnosis of ADHD at screening based on the K-SADS semistructured diagnostic interview. And a quarter of the subjects had a diagnosis of oppositional defiant disorder. About a fifth had previously been treated with stimulant medications.

I would note that stimulant medications and other psychotropic medications were washed out of subjects when they were entered into this study.

The dose of ziprasidone was flexibly titrated over the first two weeks of the study to the target dose. Now, in weeks 3 and 4 of the study, the dose could be further adjusted based on clinical judgment, up or down. In the subjects

who weighed less than 45 kilograms, the target dose was 60 to 80 milligrams a day. The actual dose range over weeks 3 and 4 was 40 to 80 milligrams, and the mean modal dose during this period was 69 milligrams a day.

In the subjects who weighed 45 kilograms or more, the target dose was 120 to 160 milligrams a day. The actual dose range achieved in weeks 3 and 4 was 80 to 160 milligrams a day, and the mean modal dose was 119 milligrams a day. Even so, two-thirds of the subjects in this weight category received doses ranging from 120 to 160 milligrams a day during weeks 3 and 4 of the study.

Now let's turn to the key results of our study. As shown on the left side of the screen, the primary statistical analysis in the ITT population of the change in YMRS total score from baseline to week 4 really a highly statistically significant treatment effect in favor of ziprasidone over placebo. The mean decrease in YMRS total score from baseline was 13.8 in the ziprasidone group compared with 8.6 in the placebo

group.

The treatment effect size, as estimated using Cohen's formula, was 0.5, and that was comparable with the treatment effect size we observed in our adult ziprasidone mania studies.

As shown on the right side of the screen, when we look at the change from baseline by each study visit and the YMRS total score for the two treatment groups, we see that the ziprasidone group separated from the placebo group as early as week 1, and that the treatment effect favoring ziprasidone is sustained over the entire four-week double-blind treatment period.

Subgroup analyses of the primary end point also showed that ziprasidone was efficacious in both males and females and in the older age group, while approaching significance in the younger age group with a P-value of .051.

The lack of significance in the post-hoc analyses in the subjects who weighed less than 45 kilograms was most likely due to the small sample size. There, we only had 31 subjects in the

ziprasidone-treated group and 14 in the placebo group, and a smaller sample size, as you know, would lead to a reduced power to detect a treatment difference. So ziprasidone was effective in subjects who weighed 45 kilograms or more.

The Clinical Global Impression of severity was an important secondary end point. As shown here, the difference in treatment effect on this end point also was highly statistically significant at the primary time point, week 4, in favor of ziprasidone over placebo. As was the case with the YMRS score, the ziprasidone and placebo groups separated on this measure as early as week 1, and the treatment effect was sustained over the entire four-week double-blind treatment period.

In terms of the overall global functioning of the subjects enrolled in this study, as shown on the left side of the screen, the percentage of subjects with a C-GAS score in the normal range at baseline was low in both

treatment groups, 2.1 percent in the ziprasidone group, 1.1 percent in the placebo group.

At week 4, the percentage of subjects in the normal functioning range had increased to 25.8 percent in the ziprasidone group compared with 15.7 percent in the placebo group. And when we look at the subset of subjects who were attending school at the end of the treatment, the percentage in the normal functioning range was 28.9 percent in the ziprasidone group compared with 4.2 percent in the placebo group.

Summing up our efficacy results, we see that a statistically significant treatment effect favoring ziprasidone over placebo was demonstrated on both the primary end point, the YMRS, and an important secondary end point, the Clinical Global Impression of severity.

The ziprasidone-treated group separated from placebo as early as week 1, and the treatment effect was sustained throughout the four-week double-blind treatment period.

Consistent treatment effects favoring

ziprasidone were also demonstrated on the Clinical Global Impression of improvement as well as a measure of global functional status, the C-GAS. Taken together, these data show that ziprasidone is effective in the treatment of children and adolescents with bipolar 1 disorder age 10 to 17, whether they present with a mixed episode or a manic episode.

Let's now review the safety data from our pediatric bipolar development program. Now, we looked at this slide before, but I'm bringing it up again to highlight the sources of our safety database. Shown on the upper right side of the screen, the short-term placebo-controlled safety database was derived from subjects who enrolled into our pivotal study, A1281132. 149 subjects were treated with ziprasidone and 88 with placebo in that study.

Shown on the bottom of the screen, the long-term safety database was derived from subjects who entered the open-label extension study, A1281133, after enrollment into our pivotal

study, 1132, or who entered the open-label extension period of study 1123 after participating in the initial three-week fixed-dose titration period of that study.

I would point out that of the 201 subjects entered into our long-term safety database, 13 subjects received doses of ziprasidone greater than the recommended dosing range. The safety data on these subjects will be presented separately. 188 subjects received doses of ziprasidone which were within the recommended dose range of 160 milligrams a day or less.

Let's begin our safety database review with the short-term controlled safety data from study A11281132. 35 percent of the ziprasidone subjects and 42 percent of the placebo subjects discontinued from study 1132. Fewer ziprasidone subjects, 4.7 percent, dropped out due to lack of efficacy compared with the placebo group which was 19-3/10 percent. But similar proportions of subjects discontinued from each treatment group due to adverse events.

Many of the adverse event discontinuations in the subjects treated with ziprasidone were related to the known pharmacologic effects of the drug. Most of the adverse event discontinuations in the placebo group were attributable to exacerbation of the underlying illness.

The most commonly reported adverse events in the ziprasidone group, which were elevated compared to placebo, are shown in this table, and include sedation, somnolence, nausea and vomiting, fatigue, dizziness, insomnia, blurred vision, musculoskeletal stiffness, restlessness and tremor.

In general, the adverse event profile of the children and adolescents enrolled in the study 1132 was similar to that seen in adults treated with ziprasidone in our adult bipolar program, with the exception of increased rates of sedation and somnolence.

With regard to the overdose events shown at the bottom of the table, I would like to point

out that five of the seven overdoses in the ziprasidone group and four of the five in the placebo group were related to dosing administration errors and were not deliberate overdose attempts.

A total of six of the 149 ziprasidone-treated subjects had nine serious adverse events, and a total of seven of the 88 placebo-treated subjects had ten serious adverse events.

The incidence of akathisia in the ziprasidone-treated subjects was 4.7 percent, compared to 1-1/10 percent in the placebo group. The overall incidence of extrapyramidal symptoms was 24-1/10 percent in the ziprasidone group and 7.9 percent in the placebo group. And the most common extrapyramidal symptoms in the ziprasidone-treated subjects included musculoskeletal stiffness and tremors.

Seven subjects each in the ziprasidone group had adverse events of extrapyramidal disorder and akathisia, and six had dystonia.

Mean changes from baseline at week 4 in our movement disorder rating scales were generally small in magnitude.

There were no completed suicides in our bipolar program, and there also was no increase in suicidality in the ziprasidone-treated group compared to the placebo group. Potentially suicide-related adverse events were reviewed by an independent panel of experts and classified according to the Columbia Suicidality Classification System, and the results showed that one subject in each treatment group attempted suicide, three subjects in each group had suicidal ideation, and one ziprasidone subject engaged in self-mutilation.

I would also like to point out that in our pediatric schizophrenia program, there was one completed suicide in an uncontrolled open-label trial. This subject was a 17-year-old female with a diagnosis of schizophrenia disorganized type who was being treated with 160 milligrams a day of ziprasidone.

Enrollment in our pediatric schizophrenia program has ended, but the data are still blinded and have not yet been analyzed.

This table shows the mean and maximum change from baseline in QTcF interval. The ziprasidone-treated patients had a mean increase in QTcF of 8.7 milliseconds, while the placebo group had a mean decrease from baseline of 3.7 milliseconds. The ziprasidone group also had a mean maximum change from baseline of 12.6 milliseconds compared to a 5.6-millisecond decrease in the placebo group, and concomitant heart rate changes were small in magnitude.

Two subjects in the ziprasidone groups had a QTcF of 460 milliseconds at any time during the study, compared with none in the placebo group. And one subject in the ziprasidone group also had an increase from baseline in QTcF of 60 milliseconds or greater. There were none in the placebo group.

To give a little more information on the two subjects with a QTcF value greater than 460

milliseconds, the first subject was a 16-year-old female who was treated with 60 milligrams of ziprasidone a day. She had a maximum QTcF on day 17 of dosing which was 478 milliseconds. This subject was discontinued from the study for prolonged QTc, and her QTcF returned to baseline value of 439 milliseconds by day 38.

The second subject was a 17-year-old male, also being treated with 60 milligrams of ziprasidone, who had a transient increase of QTcF to 461 milliseconds on day 29 of the study. All subsequent QTcF values in this subject were less than 460 milliseconds.

No patient in the study had a QTcF or a QTcB value greater than 500 milliseconds.

We have also conducted a meta-analysis to characterize the relationship between the change in QTcF from baseline and ziprasidone exposure in our pediatric and adult subjects. The meta-analysis was based on data from 18 adult trials and four pediatric trials, and provided separate estimates of the slope of the linear

regression of the change in QTcF from baseline on ziprasidone exposure in adults and pediatrics.

This scatter plot of concentration QTcF data points illustrates the range of changes in QTcF from baseline across the measured range of ziprasidone concentrations we have observed in our adult studies. Change from baseline in QTcF here is represented on the vertical axis by the distance of each data point above or below the dashed zero line. The concentration of ziprasidone increases as you go from left to right on the horizontal axis.

It is worth noting that at the zero time point, before exposure to ziprasidone, there is extensive variability in these measurements.

Here we have superimposed the concentration QTcF data observed in our four pediatric trials in green on top of the adult data. And you can see that the observed change from baseline in QTcF values for the pediatric data is similar to that observed in the adult data, and as you move across the increasing

concentrations of ziprasidone, there is no clear difference between the adult and the pediatric subjects.

The meta-analysis performed with the pooled adult and pediatric data revealed that the slopes of the relationship between the change in QTcF from baseline and ziprasidone concentration was numerically different in these two populations.

The range of the estimated slopes from the meta-analysis for the two populations in depicted in these box plots where the dot in the middle of the box represents the median point estimate of the slope.

As shown in the box on the right, the median point estimate of the slope in the pediatric subjects was .08 milliseconds per nanogram per ML. And this compares to a slope in the adult population which is estimated at .05 milliseconds per nanogram per ML, as shown in the box plot on the left.

It is important to note that the range of

the estimated slopes for the pediatric subjects does overlap the range of estimated slopes in the adult populations.

Here we are showing the estimated slopes for each of the adult -- of the 18 adult and the four pediatric studies which contributed to this meta-analysis. The pediatric studies are highlighted by the green bar.

Now, although subject population was identified as a significant covariate in the model, as you can see, there is substantial overlap in the estimated slopes, both across individual studies and across the adult and the pediatric subjects.

In contrast to what would be predicted by the meta-analysis if, in fact, this is a real difference, the actual observed mean maximal of change from baseline in our QTcF -- in our short-term placebo-controlled pediatric bipolar study is quite similar to the mean maximal change observed in special QTc studies we have conducted in adults with schizophrenia.

And in terms of the observed cardiovascular safety profile, we have seen no episodes of ventricular arrhythmias, including Torsades, and no evidence of increased syncope or palpitations in either the short-term controlled study, 1132, or in our long-term safety database.

Further, when we look at our post-marketing data, we see that the safety profile of the pediatric population is similar to the adult population. Over 2-1/2 million adults -- 2-1/2 million unique patients have been exposed to ziprasidone, including more than 350,000 subjects less than 18 years of age.

The most common indications in the pediatric subjects included bipolar disorder, followed by schizophrenia, schizoaffective disorder and psychotic disorder.

A total of ten deaths have been reported into our post-marketing safety database, but as you can see, there does not appear to be -- a total of ten deaths in pediatric subjects have been reported into the database, but as you can

see, there does not appear to be a consistent underlying pattern to these events.

There have also been no reports of Torsades, ventricular arrythmia and no cases of sudden cardiac death in pediatric patients. We have received 24 cases of QTc-related events, which are mostly prolongation. And there have been 24 reported cases of suicidal behavior or ideation.

Overall, however, based on our post-marketing data, the safety profile of the pediatric population appears to be similar to that of the adult population.

The overall incidence and pattern of abnormal labs was also generally similar between the ziprasidone and placebo groups. As would be expected, elevated prolactin was more common in subjects treated with ziprasidone -- the incidence was 12 percent -- than in subjects treated with placebo where the incident was 3 percent.

Mean changes in heart rate and blood pressure were small, and the incidence of

clinically significant changes in blood pressure and heart rate was generally similar between the ziprasidone and the placebo groups.

The mean baseline and mean change from baseline to week 4 in body weight was similar between the ziprasidone and the placebo group. 6.9 percent of ziprasidone-treated subjects compared with 3.7 percent of placebo-treated subjects had a 7 percent or greater body weight gain in our controlled study. However, there was no difference between the treatment groups in mean baseline BMI or change in BMI Z score at week 4. 98 percent of subjects in both treatment groups had less than a one unit change from baseline in BMI Z score.

This table displays the categorical change from baseline in fasting glucose and triglycerides. As shown in the top half of the table, there was no difference between ziprasidone and placebo in the proportion of subjects with normal or borderline fasting glucose levels who shifted to an abnormal level of the end of the

four-week treatment study. Only one subject in each treatment group had an abnormal glucose at the end of the study.

Shown on the bottom half of the table, 8.6 percent of the ziprasidone subjects with a normal baseline fasting triglyceride had high values at the end of treatment, compared with none in the placebo group. By contrast, fewer ziprasidone subjects who had borderline elevated triglyceride levels at baseline had elevated values at the end of treatment, 17-7/10 percent of the ziprasidone subjects, compared to 41-7/10 of the placebo-treated subjects.

Here we see the categorical change from baseline in fasting cholesterol measures. The proportion of subjects with a normal baseline total cholesterol and LDL cholesterol who shifted to an abnormally high value after treatment was negligible in both treatment groups. There was no difference between these treatment groups.

A smaller proportion of subjects with borderline total cholesterol or LDL cholesterol

shifted to high values in the ziprasidone group compared to the placebo group. And, in addition, only one of 117 subjects in the ziprasidone group who had a normal HDL value at baseline shifted to an abnormally low value after treatment, compared with five of the 74 placebo subjects.

Now, this concludes our review of our short-term safety data. Let's now look at our long-term safety data. The mean duration of exposure of subjects to ziprasidone in our longer-term safety database was 106-3/10 days and ranged from 3 to 190 days. 57 percent of subjects discontinued from long-term treatment. 20-2/10 percent discontinued due to an adverse event, and the most common adverse events leading to discontinuation included sedation, somnolence and symptoms related to the underlying illness.

The adverse event profile from the long-term study is shown in this table. It was generally similar to that observed in the short-term controlled safety database. The proportion of subjects with an adverse event of

increased weight in our long-term safety database was 5-3/10 percent.

The incidence of akathisia in the long-term safety database was 2.7 percent, and the overall incidence of extrapyramidal symptoms was 13-2/10 percent. The most common extrapyramidal symptoms included tremor and extrapyramidal disorder.

The mean change in QTcF from baseline to last observation in the long-term data set was 3-6/10 milliseconds while the mean maximum change was 8-2/10 milliseconds. And again, concomitant heart rate changes were modest. No subject had a QTcF of 460 milliseconds or greater in our long-term study. Two subjects did have an increase from baseline in QTcF that was greater than 60 milliseconds.

The first subject was a 14-year-old female being treated with 160 milligrams a day who had a maximum QTcF value of 438 milliseconds at week 10. This subject remained in the study and subsequent QTcF values were less than -- increases -- subsequent increases from baseline in

QTcF did not exceed 44 milliseconds.

The other subject was a 12-year-old female on 40 milligrams a day who had a QTcF of 431 milliseconds at week 1. Her baseline value was 365 millisecond. This subject was discontinued from the study due to a persistent prolongation of the QTc. But again, no subject in our long-term safety database had a QTcF or a QTcB greater than 500 milliseconds.

Eight male and five female subjects, ranging in age from 10 to 18 received doses of ziprasidone greater than the maximum recommended dose of 160 milligrams a day, mostly due to dosing -- dosing administration errors. The excessive doses ranged up to 880 milligrams, which was taken by one subject in a deliberate overdose attempt. All of these subjects experienced adverse events, but none of which were new or unexpected.

Five subjects had six serious adverse events, and three discontinued due to adverse

events.

In these subjects, the mean change in QTcF from baseline to last observation and the mean maximum change in QTcF was comparable to what we observed in subjects who were treated with doses within the recommended dosing range. Concomitant heart rate changes were also modest.

In terms of categorical changes, none of these subjects had a QTcF that was equal to or greater than 460 milliseconds, and none of these subjects had an increase from baseline that was 60 milliseconds or greater.

Returning now to our overall safety database, as shown on the top of the screen, the mean change from baseline in body weight was small in magnitude following long-term treatment with ziprasidone. Close to 31 percent of subjects had a 7 percent body weight gain with longer-term treatment. However, the mean change from baseline in BMI Z score was negligible, and only three of the 54 subjects who had a 7 percent or greater body weight gain had an increase in BMI Z score

from baseline that was greater than one.

None of the subjects who had a normal baseline fasting glucose developed high glucose levels after longer-term treatment with ziprasidone. 20 percent of subjects who had triglycerides in the normal range, and 40.5 percent of the subjects who had borderline triglycerides at baseline also had elevated triglycerides at the end of treatment. But close to 60 percent of subjects with high triglycerides at baseline had shifted to a normal range at the end of treatment.

Longer-term treatment with ziprasidone also had minimal effects on cholesterol, as shown here. Only three of 95 subjects with normal baseline total cholesterol of three of 124 subjects with a normal baseline LDL cholesterol had high levels after longer-term treatment with ziprasidone.

Eight of 149, or 5-4/10 percent of subjects with normal baseline HDL levels shifted to abnormally low levels following longer-term

treatment with ziprasidone.

Now, we've also done categorical change analyses of fasting glucose and fasting lipids in the subset of subjects who completed the entire six months of long-term treatment, and the results are virtually identical with the data I've just shown that includes both treaters and subjects who dropped out early from the long-term treatment study.

Treatment with ziprasidone for up to 30 weeks also was not associated with any evident effects on sexual maturation, as assessed by Tanner stage self-assessments and measurement of plasma testosterone levels. In addition, ziprasidone was not associated with any marked effects on cognitive function in either the short-term controlled trials or our long-term safety database.

From an overall safety perspective, then, ziprasidone appears to be generally well-tolerated in a four-week controlled trial in children and adolescents with bipolar 1 disorder. Ziprasidone

was also generally well-tolerated in up to 26 weeks of continued open-label treatment. There were no unexpected laboratory abnormalities, and the adverse event profile was consistent with our studies in adult patients with bipolar disorder, except for the increased rates of sedation and somnolence. And there were no new or unexpected adverse events.

Taking into consideration all of the data from our pediatric bipolar development program, our conclusions are, first, that ziprasidone has been shown to be effective in the treatment of children age 10 to 17 with bipolar 1 disorder in a well-controlled, short-term randomized clinical trial.

And, second, that ziprasidone was shown to be generally well-tolerated in up to 30 weeks of treatment with a pediatric safety profile that is similar to the adult safety profile, with minimal effects on weight and with minimal effects on metabolic status.

Thank you for your attention. I would be

happy to address any clarifying questions you may have on the data we just presented.

DR. GOODMAN: Thank you very much, Dr. Chappell. If we start lunch at 12:15 instead of 12:00 as scheduled, that would give us between 15 and 20 minutes for clarifying questions. If we can't cover everything we'd like to, we'll save those for tomorrow. So let me invite questions from around the panel.

Dr. Woolson?

DR. WOOLSON: Yes. I had a brief question about the blinding. The study is referred to as a double-blind study, and yet you have this dose titration. I was wondering how you maintained the blind since there was no titration for the placebo group.

DR. CHAPPELL: Using a double dummy -- we maintained the blind by using double dummy packaging, which allowed essentially a placebo titration, as you will, that paralleled the titration of the actual active study drug.

DR. WOOLSON: If I could just follow up

with that. As part of that titration, you indicated that there could be a faster titration on the basis of clinical judgment. I guess I was wondering how you managed that, because you would expect faster titration in the placebo group, I would think.

DR. CHAPPELL: The titration of study drug was for the most part based on clinical judgment. We provided to investigators certain parameters. For example, subjects could not be titrated up to 160 milligrams by day 7 in the -- or day 8 in the greater than 45 kilogram dose group. They couldn't reach 80 milligrams a day -- maximum dose of 80 milligrams a day in the less than 45 kilogram group by day 8.

But otherwise, investigators were urged to use their clinical judgment to flexibly adjust the dose based on the subject's presenting symptoms and the observed response in terms of efficacy and toleration over the initial titration period.

DR. GOODMAN: Okay. I'd like to ask a

question, one that was touched upon before, and I think will be a recurring theme, and it has to do with diagnostic clarity. If I understand the data that you presented, about 60 percent of the patients enrolled in the studies had mixed features. That's correct, right? About 60 percent?

DR. CHAPPELL: Yes.

DR. GOODMAN: And my question, then, is in practice, how -- could you give us some clues, perhaps, on how clinicians will make the differential diagnosis. In the context of a clinical trial, there's a lot of rigorous systematic assessment, including structured interviews, that may allow you to make that differentiation. But in clinical practice, I wonder how one -- a clinician would distinguish between mixed bipolar disorder and the kind of syndrome that Dr. Towbin was talking about before, one that might have features of irritability, maybe some attention problems, conduct problems.

So to simplify that question, were there

some cardinal symptoms or features that you think stood out that would be helpful for clinicians?

DR. CHAPPELL: Yes. Could I -- I realize -- I think you're addressing the panel. May I also speak to that as well?

DR. GOODMAN: It was for you. But I certainly invite the panel.

DR. CHAPPELL: All right. May we have slide E-109, please. Please show slide E-109.

We addressed this question by looking at the individual K-SADS items from the semistructured diagnostic interview that are specific to the diagnosis of mania. And what we found is that, while not shown on this slide, is that 80 percent of the subjects enrolled in our trial had one, if not both, of the cardinal symptoms of elation/euphoria or grandiosity.

We went further and asked what proportion had more than one of the mania-specific symptoms shown on the left side of this slide, and up to 70 percent of our subjects had four mania-specific symptoms which were currently present, based on

the K-SADS semistructured diagnostic interview at screening, 14 percent had up to three, 11 percent had up to two symptoms, and -- in general suggesting that although this was a highly comorbid or a relatively cormorbid group of subjects, that the majority had core symptoms specific to the bipolar disorder diagnosis.

DR. GOODMAN: Dr. Towbin, do you have a comment on that?

DR. TOWBIN: Just sort of a follow-up question. In that group, were those symptoms present at baseline? In other words, were those actively present at baseline, or was it a history of those symptoms?

One of the things that occurs often in the literature is people talk about a history of symptoms, and it isn't quite clear what the offset is.

DR. CHAPPELL: In the majority of cases, they were present at baseline, but for the purposes of the analysis that we just presented, we used the summary score from the K-SADS which

looks both at the child assessment and, of course, at the interview with the parent, and then provides a summary rating.

Symptoms were required to be present for the past seven days prior to screening, of course, but specifically to the K-SADS interview, we're looking here at the summary scores.

DR. GOODMAN: Dr. Vitiello?

DR. VITIELLO: In the community, a drug like Geodon is likely to be used in combination quite often with other medications. Based on what you know probably from adult data in the combination of ziprasidone and lithium, do you expect that the safety profile of the drug will be significantly affected by concomitant use of lithium? Or what can you say about concurrent use of these two drugs?

DR. CHAPPELL: We have no data in our pediatric program on concurrent use. Our data from our adult bipolar program does not suggest that there is a clinically significant risk with concomitant use.

DR. VITIELLO: Especially on the electrocardiographic changes, you wouldn't expect that combining lithium and ziprasidone will change anyway either the QT or other parameters; is that correct?

DR. CHAPPELL: That hasn't manifested in our adult ziprasidone development program, and we have not done a specific rigorous QTc study to look at that.

DR. GOODMAN: Dr. Gogtay?

DR. GOGTAY: A couple of questions. The starting dose is 20 milligrams. Is there a reason to believe that in some kids that might be already too high a dose, particularly from the standpoint of side effects?

And the second, related to that, is, have you looked at any dosage response -- or dosage relationship to the QTc interval change in terms of milligram per kilogram dosage concentration and the QTc change?

DR. CHAPPELL: To speak to your first question, which pertains to the tolerability of

the initial starting dose, we -- we initially conducted study A1281123 to explore -- to try to identify the most appropriate dose titration regimen to take in our pivotal trial. That study explored several different dose titration regimens.

The first one was actually a 10-milligram twice a day -- was a regimen that began with 10 milligrams given twice a day titrated up to 40 milligrams twice a day. And the second regimen explored was a 20 milligrams twice a day starting dose titrated up to 180 milligrams a day.

And it was on the basis of the safety and toleration data from that study in children with bipolar disorder, schizophrenia and schizoaffective disorder that a starting dose of 20 milligrams was designated as a starting dose that was generally well-tolerated.

DR. GOGTAY: And the second part, whether you've seen any dosage relationship to the QTc change?

DR. CHAPPELL: Ziprasidone is well known

to have dose-related effects on the QTc up to 160 milligrams total dose a day, but we have not analyzed that data in terms of a milligram per kilogram basis.

DR. GOODMAN: Dr. Grady-Weliky.

DR. GRADY-WELIKY: I was wondering, on the extrapyramidal symptom side effects, do you have similar data using movement disorder scales for the long-term group?

DR. CHAPPELL: We did not collect the rating scales in the long-term data set.

DR. GRADY-WELIKY: And just a follow-up to that. Were the people who experienced the EPS, were they the same in the short and long-term, and did you notice any difference in the group? I thought I read somewhere that younger children or -- were more likely to experience the EPS.

DR. CHAPPELL: If anything, the overall rates of akathisia and EPS were lower in our longer-term trial. But it is true that subjects who -- there were differences in the pattern of akathisia and extrapyramidal symptoms across

younger and older, and smaller weight subjects and older [sic] weight subjects.

For example, in subjects weighing less than 45 kilograms, the overall weight of extrapyramidal symptoms was increased -- it was about 40 percent -- compared to 19 percent in subjects that weighed 45 kilograms or greater.

In younger subjects, we also -- in the younger age category, we also saw that they had a greater incidence of dystonia and tremor and other extrapyramidal symptoms, while in the older subjects we saw a greater incidence of akathisia.

DR. GRADY-WELIKY: And final follow-up question. Any experience with the IM formulation of ziprasidone in children or adolescents?

DR. CHAPPELL: No. We have not done any studies of the IM formulation in pediatric subjects.

DR. GOODMAN: Dr. Granger?

DR. GRANGER: Related to slide 26 --

DR. CHAPPELL: May we have slide 26, please?

DR. GRANGER: -- the reason for discontinuation lost to follow-up, you note eight in the ziprasidone and one in the placebo. Can you tell us more about that and whether we have at lest safety data on the patients that were lost to follow-up?

DR. CHAPPELL: We don't have a lot of information on those subjects. And we do not have any safety data that I'm aware of on the subjects lost to follow-up.

DR. GRANGER: So do we at least know that they were, like, alive and -- I mean, do we know -- what do we know? I mean, that's a serious issue, I --

DR. CHAPPELL: Right. Let me --

DR. GRANGER: -- think. For a four-week study, that's a lot of lost to follow-up.

DR. CHAPPELL: Well, let me come back to that, if I may. There was an exit visit following -- following the last day of study drug, most subjects returned for an exit visit a week afterwards to be evaluated and to make sure their

status was stable. Most of these subjects also had ongoing established relationships with the investigators and treating physicians that had brought them into the study.

DR. GOODMAN: Dr. Robinson?

DR. ROBINSON: You reported that 1.1 percent of your patients had a greater than 60-millisecond prolongation in their QTc in your pediatric group. To help us put this in context, what's the rate from your adult studies?

DR. CHAPPELL: I'd like to ask Dr. Alderman to -- oh, that's right. Can we -- just give us a second here. May we have the data comparing our adult and -- okay. Please show slide E-5. Okay.

This slide goes directly to your question and provides the incidence of increased QTcF above certain thresholds, whether 450, 460 or 500, as well as the incidence of increase from baseline in QTcF. You specifically asked about subjects with a 60-millisecond or greater increase. And you can see the incidence in our pediatric program is

about .7 percent, which is comparable to what we've observed in our adult bipolar program.

DR. ROBINSON: Okay. On slide 53 you -- oh, this is in the long-term. So you had a rate of 1.1. And this is, like, .7. So can you sort of walk us through --

DR. CHAPPELL: If we can go back to the slide just shown, please.

These data are from our controlled studies. And the -- yes, please show slide E-5.

The duration of our pediatric trial is four weeks. The duration of these adult bipolar trials is three weeks each. So the data shown here are from our controlled pediatric and adult bipolar program. The incidence in the long-term study obviously represents uncontrolled data from subjects exposed up to six months.

DR. ROBINSON: So these are separate? These are not -- what I'm trying to get at, is this cumulative? The patients on 53 --

DR. CHAPPELL: Can we have slide 50 -- 53, please?

DR. ROBINSON: -- are they totally separate than these patients?

DR. CHAPPELL: Please show slide 53.

DR. ROBINSON: Here you have the 1.1 percent --

DR. CHAPPELL: Right. Here we have two subjects with an increase from baseline. These are not cumulative from the previous study. This refers to the incidence of categorical changes observed in our long-term extension study.

DR. ROBINSON: Okay. So this would be on top of --

DR. CHAPPELL: On top of what we previously reported for the short-term controlled study.

DR. ROBINSON: Yeah. So what would be the equivalent adult rate for that?

DR. CHAPPELL: We -- I --

DR. ROBINSON: You don't know?

DR. CHAPPELL: I'm not sure that we have that information with us, but we would be happy to obtain it and provide it to you.

DR. GOODMAN: Dr. Cnann?

DR. CNANN: Yes. I actually wanted to follow up on Dr. Granger's question with regard to slide 49, which is almost the same question on the long-term. Slide 49 --

DR. CHAPPELL: May we have slide 49, please.

DR. CNANN: It shows 57 percent discontinued of which, I assume, the 20 percent is adverse events. That still leaves about 37 percent discontinued. What do you know about them?

DR. CHAPPELL: Are you asking about what we know about the reasons for discontinuation?

DR. CNANN: Yes. Precisely.

DR. CHAPPELL: The reasons would encompass a variety of things, including lack of efficacy or predominantly being lost to follow-up, and -- but we don't have more specific information about these other discontinuations or -- it could also encompass being non-compliant with the protocol. It's a variety of miscellaneous

reasons.

DR. CNANN: Do you discontinue due to non-compliance with the medication or with the follow-up schedule of measurements of the protocol?

DR. CHAPPELL: It could be both, depending on the given circumstances.

DR. GOODMAN: Do you have concerns about that?

DR. CNANN: I guess it appears to me that if about a third of the patients on the long-term discontinued without it being specified as an adverse event, without it being known, yes, I do have somewhat of a concern of what happened here.

DR. GOODMAN: Does the FDA share any concerns about that issue? Don't want to put you on the spot.

DR. LAUGHREN: I'm assuming that somewhere the company must have data on why those patients left at that point. I mean, you have data on those who left for adverse events, so --

DR. CHAPPELL: Right. We have the data

and we'll be happy to provide it to you.

DR. GOODMAN: Dr. Towbin and Dr. Gogtay, and that's it, before lunch.

DR. TOWBIN: I'll try to be brief. So Dr. Cnann has actually landed on a concern that I had, so if we could go back to slide 49. So it appears that a majority of subjects in this long-term study discontinued, and in looking at the adverse event, I was a little bit puzzled that you had four individuals who had adverse events discontinued because of, quote, bipolar disorder, unquote. And then, down below, you list mania for two, and I was wondering what you meant by that. How is it that they would discontinue because of bipolar disorder and that mania was a separate thing? Could you explain?

DR. CHAPPELL: Yeah. These terms are simply the terms assigned by the principal investigator as they were reported and then mapped within our MedDRA system of reporting adverse events, but I take your point that the two subjects with mania obviously represent bipolar

disorder.

DR. TOWBIN: So that would be six individuals -- and does that mean that there was a deterioration in their symptoms while on the drug?

DR. CHAPPELL: It does point to an exacerbation of symptoms, yes.

DR. TOWBIN: While they were on the drug?

DR. CHAPPELL: Yes.

DR. TOWBIN: And the other thing I wanted to go to, if we could, is slide 19.

DR. CHAPPELL: May we have slide 19, please?

DR. TOWBIN: Here you offer an effect size of 0.5, and I believe this is for the combined population, so the entire age group. I was wondering if you did a separate analysis of the effect size for the younger age group and an effect size for the older age group, and what that might be.

DR. CHAPPELL: That is an important consideration, but we have not done that analysis yet.

DR. GOODMAN: Dr. Laughren?

DR. LAUGHREN: Well, the question about patients discontinuing in a large open cohort because they became symptomatic, really that's sort of getting at the question of whether or not this drug has maintenance benefits. And to get at that, you really have to do a specific trial. You know, we usually like to see a randomized withdrawal trial where some continue on drug, some go to placebo, and you look at time to relapse.

I don't think that -- has that been done in adults yet with bipolar?

DR. CHAPPELL: Yes, we have completed an adult maintenance trial, which is currently under review by the agency, and the results of that study indicated a positive maintenance effect for ziprasidone.

DR. LAUGHREN: So I would argue that that's the better way of getting at --

DR. CHAPPELL: Right.

DR. LAUGHREN: -- the question.

DR. CHAPPELL: If I may add, we do have -- we do have information on the YMRS scores

of subjects who continued into the long-term treatment study showing that the subjects that were on ziprasidone before moving to the long-term extension trial maintained their treatment effect throughout the six-month period, and the subjects that were on placebo before entering the long-term trial had a numerical decrease in symptoms, and that effect was maintained throughout the study, too, as shown on slide E-130. Let's share this with the audience.

So this -- this -- shown here are the data collected on the YMRS end point across the open-label extension trial. The blue line represents the subjects who were on ziprasidone and continued on ziprasidone. The yellow line shows the subjects that were on placebo and then switched over to open-label ziprasidone. And you can see a numeric decrease from their baseline scores, which are sort of noted in the left corner of the slide.

The placebo group had a baseline mean

YMRS prior to entering the long-term group of about 20.

DR. GOODMAN: Dr. Gogtay, then lunch.

DR. GOGTAY: I will be brief. This is actually a follow-up to Dr. Towbin's second part of the question. On slide 20 -- if we could have that --

DR. CHAPPELL: May we have slide 20, please?

DR. GOGTAY: If you see on the slide for kids who weighed less than 45 KGs, there is no significant effect, and these kids are likely to be younger kids. And if you look at age 10 to 14, it's barely significant. So I was wondering if it's not an effective in the younger children, and whether you have looked at age as a continuous measure and see age response relationship to this.

DR. CHAPPELL: Let me first respond to your question about looking at age as a continuous measure. We haven't done additional analyses around age based on continuous measure of age.

With regard to the question of efficacy

in the subjects who weighed less than 45 kilogram -- may we have slide E-122, please? I think that's it. Yes.

This -- shown here are the subjects weighing less than 45 kilograms who were entered into the ziprasidone and the placebo treatment group. 26 completed in the ziprasidone group, and eight in the placebo. Six subjects -- eight dropped out in the ziprasidone group and seven in the placebo. And what I would like to point out is that two of the eight who dropped out in the ziprasidone group dropped out due to lack of efficacy, compared with six of the seven in the placebo group.

In addition, we've looked at the responder status of the subjects that continued on treatment -- and if we could have slide 123, please.

This plot shows the proportion of subjects in the less than 45 kilogram group treated with ziprasidone and placebo who had a 50 percent or greater decrease in total YMRS from

baseline to the end of treatment, and you can see that about half of the subjects on ziprasidone reached -- had that responder status, compared to about 20 percent of the subjects on placebo.

Based on these post-hoc analyses, we believe the results support our view that the primary reason we did not see efficacy in the less than 45 kilogram group was sample size, that if we had additional subjects and greater power, we feel that we probably would have seen a statistically significant effect.

And it's important also to bear in mind this study was not designed nor powered to look at these subgroup analyses and to detect these differences.

So overall, if you fold these results into the overall picture of ziprasidone in these subjects, we think it supports our conclusion that subjects less than 45 kilograms should also be considered as a candidate for treatment with ziprasidone.

DR. GOODMAN: Thank you very much, Dr. Chappell. We're going to break for lunch at

resume at promptly 1:15.

(Whereupon, at 12:19 p.m., a lunch recess was taken)

AFTERNOON SESSION

(1:14 p.m.)

DR. GOODMAN: Okay. We're resuming our meeting. We'll proceed now with a presentation by Eli Lilly. I turn it over to you.

DR. BAKER: Hi. On behalf of Lilly, I'd like to thank the FDA for this opportunity to present our olanzapine research, but especially I want to express gratitude to the committee. We recognize that you're taking time away from your own work and away from your own lives in this public service, and the sponsors appreciate that.

My name is Robert Baker. I'm a psychiatrist at Lilly, and I'm the leader of the team that's responsible for global development of out antipsychotic drugs, including olanzapine. And I'm here to introduce Lilly's presentation.

Let's start with, why study olanzapine for adolescent patients with schizophrenia and mania. We heard from Dr. Vitiello this morning that these disorders -- a substantial minority of patients who are going to have schizophrenia and

bipolar mania have their onset before they're adults. So there's a clinical need. Those patients are there. There are clinicians that are trying to treat those patients.

We know that the rationale behind a lot of the efforts that the government has taken to encourage us to develop more research-based guidance for clinicians treating adolescent patients is in recognition of that need, and in that sense it's a very good thing that you're seeing three sponsors of atypical antipsychotics with information about treating pediatric or teenaged children today.

In addition, we all know that schizophrenia and bipolar mania would be on almost anybody's list of the most severe and the most disabling of psychiatric illnesses, and yet we've also heard several times this morning that when they occur in younger patients, in patients who aren't yet adults, the outlook is even worse, and it's even worse because it can be so hard to achieve efficacious results.

So as we were developing olanzapine years ago and recognizing the efficacy in adult population, we began to undertake investigations, preliminary exploration, in pediatric patients even before the initial approval in the U.S. So let's review next a little bit of the regulatory background that takes us to where we are today. Olanzapine was first approved in the United States for treating schizophrenia at the end of 1996. We started a dialogue with the FDA in 1999, culminating in 2001 with a formal request that was requesting or describing the research program that you now see in front of you, across a variety of different investigations.

That was completed and submitted to the agency in 2006. We've subsequently received approvable letters.

Importantly, separately, we've also had request from the agency to do new analyses, more analyses on existing data regarding weight gain and metabolic adverse events, which are important questions for olanzapine. We conducted that -- a

large analysis project across 2007 and 2008, and that information was reflected in updates to the olanzapine U.S. package labeling in '07 and earlier this year.

Those updates -- much of them are about adult patients. Much of it is about describing weight, metabolic and glucose impact within subgroups, but it also includes adolescent patients, and I raise that in part because, as you look at the data in the briefing document and that we present this afternoon, much of that is from those 2006 submissions, but when it comes to weight, lipid and glucose, what you'll see is reflecting these more recent and most current analyses that we have, and it is what is reflected currently in olanzapine U.S. labeling.

I'm joined by a couple of my colleagues today who will walk through in more detail the data, but let me pre-empt them a bit by jumping to the overall conclusions. They are that, as you might expect, given the efficacy that is available to adults, our studies in teenagers demonstrated

efficacy for treating symptoms of acute schizophrenia and acute bipolar mania.

In addition, as you might expect, qualitatively, the adverse event profile looked similar to what we see in adults. But interestingly and strikingly, for some of those adverse events -- especially for weight gain; also for lipids -- the magnitude or the frequency of adverse outcomes were greater in adolescent patients that we are accustomed to seeing in our adult studies.

That leads to a conclusion that, for many patients, because of those adverse events, olanzapine is not likely to be the optimal choice.

On the other hand, given the clinical need with these severe illnesses and patients who don't respond well to it, and patients whose early lives can be so disrupted by the need for better efficacy, there is, given the efficacy, potentially a very important role for those subgroup of patients for whom that hope of efficacy could offset the adverse events that we

see.

That leads to a conclusion that it is a valuable option. And it also, I think, was part of what the FDA was considering as the FDA proposed to us that if these indications are approved, they would be for second-line treatment status.

In your handout and on the screen are outlines of what that language would be, but Lilly accepted this proposal, accepted it because it appears to be consistent with our priorities, which are to better inform clinicians treating these patients about the research that can sharpen their own treatment decisions, risk/benefit decisions, as well as supporting availability of the medication for those subgroup for whom the efficacy -- benefit the efficacy needs are so important.

As I mentioned we will give you much of the detail behind that, and to do that I'm joined by two other psychiatrists who are also employed by Lilly. First you'll hear from Dr. Olawale

Osuntokun. Dr. Osuntokun is the global lead physician for Zyprexa, and he's going to review the results from our olanzapine clinical trials from an efficacy standpoint.

Next you'll hear from Dr. Robert Conley. Dr. Conley has a long career as a schizophrenia researcher based here in Maryland, but joined us at Lilly a year and a half ago, and he's going to speak directly to the safety results of our studies as well as talk about Lilly's proposed risk management plan should these indications be approved.

And then, finally, I'll come back with some summarizing and concluding comments to address the overall risk/benefit.

Dr. Osuntokun?

DR. OSUNTOKUN: Thank you, Dr. Baker. Good afternoon to you all. My name is Dr. Olawale Osuntokun. My medical background is in general adult psychiatry, which I practice in various health settings that cared for individuals diagnosed with the same disorders that have been

discussed today.

Currently, as mentioned by Dr. Baker, I am a clinical research physician as Lilly, and have been so since 2005. Today I'll be reviewing with you two trials of olanzapine in the treatment of adolescents. Both studies have been published in peer review journals.

The first is the schizophrenia study, the adolescent schizophrenia study, designated as study HGIN, a multi-center study conducted in the United States and in Russia, and I'll review with you the following from study HGIN.

First is the study design which comprises of three phases. The first, patients are screened to ensure consistency with the inclusion and exclusion criteria. With their physicians patients are provided 2 to 14 days to be tapered off medications not allowed in the subsequent periods, with an option of 21 days for those particular medications that may require a longer taper period.

Study period 2 is a six-week double-blind

placebo-controlled period, with patients randomized in a 2-to-1 ration to either olanzapine or placebo, respectively. Patients are then started on 2.5 milligrams or 5 milligrams of olanzapine, based on investigator discretion and clinical need, with an initial titration up to 10 milligrams by the first week to prevent underdosing but yet take into consideration tolerability issues.

Through the subsequent parts of the study, patients are flexibly dosed 2.5 to 20 milligrams of olanzapine consistent with the label and also consistent with clinical direction provided to us by clinical experts.

This was later confirmed by PK data showing comparable overlap between exposures in adolescents and adults, some differences in exposures which could be explained by differences in weight and smoking status.

Study period 3 is a 26-week open-label period with a similar dosing strategy, flexibly dosed, 2.5 to 20, during that period. Patients

completing study period 2, as well as those who did not achieve response by the third week during the acute phase, were able to be enrolled in this open-label period.

In total, 107 patients were randomized to study HGIN, with its primary objective to assess the efficacy of olanzapine in comparison to placebo as measured by the Brief Psychiatric Rating Scale, the children's version, which I'll refer to as BPRS-C, which has been validated to be used in this patient population. This is a scale that contains 21 items that measures a variety of behaviors of symptoms characteristic of schizophrenia, such as disturbances in behavior, thought abnormalities, disturbances in mood, social withdrawal, anxiety and even cognition.

As -- listed here are other secondary measures that were assessed during study HGIN.

The main inclusion criteria had patients by the first visit, or screening visit, meet the age of 13 to 17 by that visit. At the screening visit, as well as the randomization visit,

patients then had to meet the diagnostic criteria as well as a severity criteria: A diagnosis of schizophrenia based on DSM-IV criteria, similar to what's used to diagnose adults with schizophrenia, as we heard earlier on.

This is confirmed with the Kiddie Schedule for Affective Disorders and Schizophrenia, obtaining both present and lifetime information. The severity criteria was a score on the BPRS-C of at least 35, indicating these patients had moderate to marked symptomatology. Patient also had to have prominence with a score of at least three on items such as hallucinations, delusions or peculiar fantasies.

These criteria indicated these patients had a clinical need for treatment to be justified for enrollment in this study, either a need for treatment or perhaps a need for change because of these persistent symptoms despite treatment prior to coming into to study.

In order to -- in addition to the inclusion criteria, to enroll the appropriate

patient population, certain diagnostic categories were excluded, such as those with major developmental disorders or other psychiatric illnesses as listed. Those judged to be at serious risk of suicide, with acute or unstable medical illnesses, or those with clinically significant abnormal laboratory findings were also excluded.

Key baseline patient characteristics are presented here, comparing both treatment groups, olanzapine and placebo. There were no differences between the two groups. However, these key characteristics are very representative of the typical patient seen in the usual practice setting.

Completion and discontinuation rates are presented here, which also provide to us useful measures of effectiveness by assessing discontinuations due to reasons that are particularly important and clinically relevant, reasons a physician and a patient may deal with on a daily basis that may result in that patient

either continuing that treatment or perhaps discontinuing it. As we can see, those treated with olanzapine in this study had higher completion rates compared to those treated with placebo.

Not statistically different was the adverse event numerically higher in olanzapine compared to placebo. Of importance, in terms of efficacy, is the fact that over half of the patients treated with placebo discontinued due to lack of efficacy compared to a lower rate on the olanzapine treatment group. These benefits are important and underscore the benefits overseen seen in olanzapine, which has also been documented in the adult program.

These are consistent with the primary findings, which I will share on this slide that showed the changes in the BPRS-C score from baseline in blue to end point in orange in the BPRS-C scores following six weeks of double-blind placebo-controlled treatment.

Mean daily dosing for olanzapine is 11.1

milligrams. Note, olanzapine changes are on the left and placebo on the right.

The dashed line that you see represents the entry score criteria, which I mentioned earlier on, indicating these patients had significant, moderate or marked symptomatology. Again, these patients had a clinical need justification for enrollment in this study.

When -- in fact, looking at the baseline mean scores for patients in both treatment groups, a score of 50, these patients' symptoms at baseline were actually severe. This is consistent with literature provided by Hughes and colleagues that dictate a score of above 42 represents severe symptoms. These are patients or a teenager who might have prominence -- as we discussed earlier on -- in hallucinations where they may hear voices that command them, make derogatory statements about them, speak badly about them, or generally run commentary that are very interfering.

This might also be in the form of delusions where they may develop persecutorial

beliefs that people are out to get them or harm them, peculiar thoughts or fantasies, may take on bizarre themes that are total incomprehensible to those around them. These are individuals that are significantly impaired by such symptoms.

What we see after six weeks of double-blind treatment, those treated with olanzapine had a statistically significant reduction, 19.3 points, compared to those on placebo, a 9.1 point reduction. This corresponds to an effect size of .63, which is clinically meaningful when, in fact, compared to that reported in similar adult studies, although caution has to be taken in making such comparisons, as these are not head-to-head. An effect size of .57 has been reported in that patient population. This is a population that olanzapine's benefits have also been well-established.

So for these patients with significant symptoms, what else does this mean clinically to the individual patient? These are symptoms

looking at the end point score where it's been reduced to a level that would no longer be considered severe. The magnitude change is also almost 20 points, which is almost twice what would be considered minimum improvement, which has also been described by prominent researchers, Leutch and his colleagues, as a BPRS-C absolute change of 10, representing minimum improvement. These improvements were not seen on those patients treated with placebo.

Also, when you compare these patients to their baseline scores, and also that clinical need for treatment, these patients had improved significantly, where 60 percent of patients on olanzapine compared to 40 on placebo had dropped below that entry severity criteria.

It is due to these benefits, consistent with the previous slide, that when these patients experience these benefits, they are not likely to discontinue due to efficacy-related reasons. These patterns of improvements are shown here on the visit-wise analysis over time -- and this is

an MMRM analysis which, at end point, is consistent with the previous analysis I showed, which was at last observation carried forward.

We can see olanzapine -- those treated on olanzapine had statistical advantages in the magnitude reduction by the second week, sustained through four weeks of additional double-blind placebo-controlled treatment.

Secondary efficacy outcomes provide additional evidence of efficacy. Looking at symptom reduction as well as improvement, using the PANSS scale, using the Clinical Global Impression scales, and all other parameters. Those statistically significant are highlighted, showing olanzapine's advantage over placebo.

We did conduct additional efficacy analyses, looking at BPRS change in certain subgroups and their interaction. None of these interactions were significant, and subgroups include -- the subgroups looked at include age, gender, ethnicity, as well as country.

We did, however, find a difference in

treatment effect between the population in the U.S. and the population in Russia, with an effect size for those in Russia of .96 compared to an effect size of those in the U.S. of .32. This was driven by largely a disparate placebo response, which was low in Russia and quite in the United States.

In an attempt to understand these findings, which have also been reviewed with the FDA, we carried out a number of exploratory analyses, none of which provided a clear explanation for this finding.

I do want to remind you that this study was designed to look at the treatment differences in the overall population, and not designed specifically to assess differences between these subgroups.

The FDA, as we have, concluded that the overall results do indicate that olanzapine is an effective treatment in adolescents diagnosed with schizophrenia.

So from our study HGIN, I would conclude

that olanzapine has demonstrated efficacy in treating this patient population diagnosed with schizophrenia, with an average of 10.2 points advantage over placebo. An effect size corresponding to be .63, comparable to that seen in the adult population, where its efficacy has been well-established.

Secondary measures were also consistent with the primary measure in showing benefits over six weeks of double-blind placebo treatment. These are critical achievements in the acute control of psychosis for a chronic prolonged lifelong disorder.

I will now switch gears and present to you the adolescent bipolar study designated as study HGIU, also a multi-center study, conducted in the continental United States and in Puerto Rico.

The study design is similar to the adolescent schizophrenia study, with the exception that the acute double-blind placebo treatment phase was three weeks. Similar dosing was

employed in this study, as well as the dosing strategy. Patients enrolled in the open-label period, the criteria for enrollment was also similar as in the schizophrenia study.

In total, 161 patients were randomized in study HGIU. Its primary objective to also to assess the efficacy of olanzapine in comparison to placebo, using the Young Mania Rating Scale in adolescents diagnosed with manic or mixed symptoms, may be psychotic or may have associated psychotic symptoms or non-psychotic symptoms. I will refer to the Young Mania Rating Scale as the YMRS scale.

Listed here are other secondary items evaluated during the course of study HGIU.

Similar to the schizophrenia study, an age requirement of 13 to 17 was with study HGIU by the first visit or screening visit. Also, patients had to meet a diagnostic and severity criteria at both screening visits as well as randomization visit. A diagnosis of bipolar 1, using the DSM-IV, again, confirmed by structured

interview guide as the use of K-SADS, obtaining both present and lifetime information, similarly used to diagnose adults with bipolar type 1.

Patients had to meet, at both screening and randomization, current manic or mixed symptoms. A YMRS score also required at both visits of at least 20, again, indicating significant symptomatology. And these patients had that same clinical need for treatment, or perhaps a change in treatment due to persistent symptoms prior to coming in to this study.

In addition to the inclusion criteria, to also ensure that the appropriate patient population was enrolled, certain diagnostic illnesses were also excluded. Of note, as with similar discussions earlier on, patients with ADHD were not excluded, given the fact that this is a highly comorbid condition with bipolar, but as we try and recognize, these are distinct entities.

Patients with certain psychiatric and medical risks were also excluded from study HGIU.

Key baseline patient characteristics are

presented here, comparing the two treatments. We do see some statistically significant baseline differences, and those are highlighted on this slide. Again, these characteristics typify that patient who is seen in the usual treatment practice setting.

Completion and discontinuation rates are also provided. Higher completion rates in those treated with olanzapine compared to placebo, but only lack of efficacy with those treated with placebo having a higher discontinuation early due to lack of efficacy compared to olanzapine, again, underscoring the benefits of olanzapine in this population when they do receive improvement, are not likely to discontinue due to efficacy-related reasons. These findings, like in the schizophrenia study, are consistent with the primary findings, looking at changes in YMRS from baseline to end point.

Baseline scores here again are represented in blue, olanzapine on the left, and end point in orange. Placebo-treated group is on

the right. The mean daily dosing in this study was approximately 9 milligrams per day. The dashed line, again, representing the entry severity criteria of at least 20, indicating these were patients with significant symptomatology. And looking at their baseline scores also, a minimum of at least 30, these were patients with very prominent symptoms. Typical symptoms of mania when prominent, as we've heard earlier on, may include flight of ideas, racing thoughts where individuals are barraged with disconnected streams of ideas, leading to perhaps a disorganization in their speech, in their thinking or their behavior.

Patients may also develop, as an example, elated ideas or elated feelings, grandiose ideas, which may impair judgment or even result in risk-taking behaviors.

Following three weeks of double-blind treatment, those on olanzapine demonstrated a statistically significant improvement in the reduction of YMRS by 17.7 points, compared to those treated with placebo of 10 points. Again,

this corresponds to an effect size of .84 which, in fact, when compared to an adult population -- similarly designed study, but again, with caution in comparison -- an effect size in those studies have been reported to range from .46 to .53.

This a larger effect seen in this adolescent patient population. Also, when you compare the significant reduction from baseline to end point, a statistically significant -- and twice more patients on olanzapine had a reduction below that entry severity criteria, which was described earlier on, the dashed line that we see of at least 20, indicating these patients, again, had a meaningful change from the point of entry into this study to the point -- at end point, basically.

Again, due to these benefits, these are reasons that would explain why patients on olanzapine are not likely to discontinue treatment due to efficacy-related reasons, as in this study, following three weeks, better than those treated with placebo.

These patterns of improvements have also been demonstrated, looking at the visit-wise analysis, again, an advantage in those treated with olanzapine from the first week, with additional two weeks of double-blind treatment sustaining that benefit and advantage over placebo.

Additional evidence of efficacy has also been demonstrated looking at other ways of measuring benefits, showing a significant reduction, or significant improvement. Remission and response rates are also better. Those that were statistically different have been highlighted.

We have also looked at the incidence of switching to depression, which is an important clinical scenario in treating acute episodes related to bipolar. This is either because of the anti-manic effect of the agent, or as the natural course of this illness.

In looking at this, the incidence of those on olanzapine that switched to depression,

those were patients who -- those analyzed in this were those who were non-depressed at baseline who then met the criteria for a switch. These rates were lower, although not statistically significantly different from placebo, indicating that olanzapine, as an effective anti-manic agent, following three weeks of double-blind treatment, does not worsen or cause a switch into depression.

So in conclusion, study HGIU has been shown to be efficacious in treating individuals, adolescents, with bipolar episodes, acute manic or mixed episodes, with an average advantage of 8.2 points over placebo, corresponding to an effect size .84, larger than that seen when compared with caution in a similar reported adult population where olanzapine's benefits have been well-established.

Secondary measures also are consistent with the primary measures, showing that these benefits coincide and are similar to what was shown, looking at the YMRS score.

These benefits explain why patients do

not -- or are not likely to discontinue treatment due to efficacy-related reasons.

So, overall, our conclusion is that the results from both studies were positive. Data presented support that olanzapine is an effective agent in treating acute symptoms related to bipolar type 1, as well as acute psychotic symptoms related to schizophrenia. To these individuals who we've heard from our experts are vulnerable, who, in their formative years, may be struck by symptoms that make them lose touch with reality, experience unpredictable mood symptoms that are characteristic of acute bipolar symptoms, this study result does offer those who will benefit from olanzapine hope -- and olanzapine as a treatment option in this patient population.

I will now call upon my colleague, Dr. Robert Conley, to provide us an overview of the safety findings.

DR. CONLEY: Thank you, Dr. Osuntokun.

Good afternoon, and again, I'd also like to extend my thanks to the committee and the FDA

for their work and attention to this important matter. I am Dr. Rob Conley. I have worked at Lilly for about a year and a half now in the position of a Lilly scholar, which means I am a senior consultant to the company, for psychosis and related disorders. And as Dr. Baker has mentioned, I've worked as a schizophrenia researcher for many years at the University of Maryland where I remain an adjunct professor in psychiatry and pharmacy science.

And I've been really interested in the area of treatment of psychotic disorders for my whole career. In fact, it's interesting -- my group was one of the first to report in '98 that the use of antipsychotics, particularly second-generation antipsychotics, was associated with weight gain. So I've been doing this for a while.

I'm going to share with you today the data regarding the safety of olanzapine in adolescents from our clinical trial and our longer-term observational database.

Olanzapine itself has a well-characterized safety profile for a number of reasons. One is because it's been marketed in 109 countries since it was introduced in 1996. It's been used in more than 27 million patients in that time. And, of course, Lilly has provided safety and surveillance data and updated its product label continuously since that time.

My talk today is going to focus really on the adolescent data, but it's important to know, in comparing to our adult data, which we have done, we see similar types of adverse events in adolescents to adults, but the incidence and magnitude of weight gain, elevation in triglycerides, cholesterol levels are greater in adolescents than adults. And safety data, hepatic enzyme changes and prolactin elevations are more common in adolescents than they are in adults.

The studies that provide the data for what I'm going to show you today are these six that you see. The first two are the studies that Dr. Osuntokun had shared with you regarding the

efficacy in adolescents with schizophrenia or bipolar disorder. The data is, of course, from both a double-blind comparison trial as well as a 26-week open-label continuation.

Also, there are two other studies, as you see there, HGMF and LOAY, which are 4-1/2, and then a 24-week open-label study. And then, finally, there are two studies that weren't in adolescents only, but included adolescents and adults, but were double-blind placebo-controlled studies that we felt also could provide informative data for our overall metabolic database, which I'll tell you about in a moment. And so the adolescents from those studies were also included in the data that we're going to show you today.

How these things are put together is that some of the slides I'll show you are from our so-called submission adolescent placebo-controlled database. That's those two studies you were presented. Median exposure, 22 days there. And also the submission adolescent overall database --

and that's the two studies, plus those next two on that slide -- and now it's the full exposure time where median exposure was 99 days on the drugs.

That was in our submission. And now, since that time, as Dr. Baker has alluded, more studies have gone on and been completed and been added into the product label. So in order to provide you all as complete and up-to-date data as we can, we have shown a number of studies or slides that will actually use this metabolic adolescent placebo-controlled database and the overall integrated database -- and the difference, really, are those other 45 patients have been added in, but it provides a little bit more data to look at the safety of the medication.

I'm going to cover a number of topics today, adverse events, weight gain, glucose, lipids, et cetera, that we think are important to consider in understanding the safety profile of this medication.

First, looking at serious adverse events in essentially the traditional way, in our

placebo-controlled databases where you can make this direct comparison, patients with one or more serious adverse event -- you see with olanzapine 3.4 percent of patients, placebo 1.1 percent. And the breakdown being mostly exacerbations of underlying disorder.

In looking at the serious adverse events overall in the overall exposure database -- now, this, of course, is olanzapine only -- you see 7.7 percent of patients had one or more SAE. Again, an exacerbation of underlying disorder was the most common thing that we were seeing happen.

You see here also suicidal ideation and suicide attempt. We know that's also an important consideration, so just to flesh that out a little bit more, in the placebo-controlled database we had three possible suicidal behavior ideation events. Two were on olanzapine, which was one suicidal ideation and one self-injurious behavior, and one on placebo, so not much of a difference there.

And, furthermore, in the bipolar data --

in the bipolar direct placebo comparison where suicidal ideation was rated, there was a minor improvement, not a significant one, in olanzapine and placebo. But importantly, no difference be olanzapine and placebo in those groups.

Looking another way at this, discontinuations due to adverse events in our submission databases, you see an overall discontinuations -- again, 4.5 percent of olanzapine-treated patients, versus 1.1 percent with placebo. Overall exposure, 11 percent. You see a difference.

And, again, in thinking of these discontinuations, one thing we thought of, with your questioning this morning, is that you had been interested in completion, not just discontinuation rates, so to say that, 55 percent of patients completed the overall exposure. This was with the median time in trial of 302 days. And four discontinuations, 11 percent, were adverse events. 11 percent lack of efficacy. 2.9 percent lost to follow-up. 7 percent patient

decision. Then there were smaller things other than that.

Another way to look is treatment -- treatment-emergent adverse events, and we're separating that by those that are reported in more than 5 percent of olanzapine-treated patients. And you can see here with one or more treatment-emergent event, 88 percent of olanzapine-treated patients, 60 percent of placebo, with sedation-related events, increase in weight, increase in appetite and liver enzyme changes as being the conditions that separate out between olanzapine and placebo.

Looking at the overall database -- now, of course, with olanzapine-only subjects -- again, 83 percent had at least treatment-emergent adverse event, and again, with sedation, weight increase, increased appetite -- a similar breakdown that you saw in the placebo-controlled trials.

Now looking at things a little more specifically, weight, height and BMI. In our placebo-controlled database, weight change, 3.9

kilograms for olanzapine, .2 for placebo. That was significantly different. And BMI, a change of 1.2 points versus .1 points -- again, a significant difference between the two groups in the acute placebo-controlled database.

Also important to think about is what's really happening in people who take olanzapine, so another way to look at this is the distribution of weight change in this adolescent submission placebo-controlled database. The top histogram is olanzapine and the bottom one is placebo. And you can see the two dotted lines there are at zero percent no change and 7 percent, which is considered the clinically significant cutoff.

And you can see from this 43-1/2 percent of olanzapine-treated patients had 7 or more percent weight gain. The distribution is peaking around 6 percent, with a relatively normal distribution. Placebo you can see is more or less a normal distribution around no change. There are some outliers in both groups.

Also looking at weight -- now, this is

what's currently reflected in our label, and here I'm going to move to that largest database that I told you about to provide you the most data.

You see the difference in mean weight change with olanzapine versus placebo in placebo-controlled studies, and those clinically important break points, 7 percent and now also 15 percent. You see more patients with olanzapine than placebo in both of those groups also.

With weight -- again, this is in the longer-term olanzapine-only group -- weight gain of 11.2 kilograms, and then the cuts of 7 percent, 15 percent and 25 percent, and how many subjects met those criteria in each of those groups in longer-term exposure, 89, 55, 29.

Moving from weight to glucose changes. Now, here we have, again, our less than 12-week exposure, but again, we're looking at, now, our labeling, which is based on that larger database. Olanzapine, an increase, 2.7 points on glucose versus a slight decrease with placebo. And we've also, as the agency has requested, done shift

changes. And you can see normal to high and borderline to high. Not much there in the normal to high group, but borderline to high is where you see a signal with olanzapine.

And one important thing to note in looking at this is the -- of course, subjects had to be borderline at the beginning to have this possibility for risk. And that was only true of 14 olanzapine and 13 placebo-treated patients. So it was relatively small number in that group, but still the borderline group is where you see the more shifts.

Also in the longer-term database, 3.1 points of olanzapine change in blood sugar. And again, you see the normal to high and the borderline to high group. More shifts from borderline to high.

Moving from that to hemoglobin A1c and urine glucose, in our adolescent studies, hemoglobin A1c was only collected in patients who had known diabetes. There were 24 of those subjects. None had shifts from normal to abnormal

hemoglobin A1c.

For treatment-emergent glycosuria, in the placebo-controlled database, .6 percent of olanzapine-treated adolescents -- and this is at any time -- had this versus no placebo-controlled patients. Same .6 percent in the longer-term overall integrated database.

Looking at total cholesterol now, you see here -- again, this is in our labeling and in the larger metabolic database -- mean change of 12.9 milligrams per deciliter versus the 1.3 for placebo. And, again, normal to high versus borderline to high, you're seeing more shift and a significant shift in the borderline to high group.

Looking at total cholesterol in the overall exposure, 5.5 points of change. And again, more shifts in the borderline to high group, percentage-wise.

Looking at LDL cholesterol, again, with placebo comparison, 6.5 points of change versus 1 for placebo. And again, the shift -- same pattern you're seeing with more shifts in the borderline

to high group.

In all of these cases, that borderline to high group, of course, is again from a smaller cell size, but nevertheless, that's where you're seeing more of the shifts.

In the overall exposure, again, olanzapine, 5.4 points, normal to high, borderline to high. Again, a similar pattern with more changes in borderline to high.

HDL is like what we see with other things -- not much change between olanzapine and placebo, either in mean change difference or the incidence of change of shifts.

And the overall exposure, a slight decrease now in HDL levels, and a slight -- well, not slight, 21 percent borderline going to low, again, the borderline group being the one that's likely to change.

In this -- in the past few slides, the one thing I should mention is that our -- although the slides you just saw were correct, in the handout you have there's a minor typo where, in

the last line, there's a greater than or equal to sign for one of the cutoffs; it should be just a greater than sign, so I'd like to mention that. And that was in slides 50 to 53. Sorry I didn't say that when they up. Just missed that. But, again, slides up there are right. Just different in your handout.

So, again, fasting triglycerides -- as we mentioned, with a less than six-week exposure, you see the median [sic] change between olanzapine and placebo, and again, the shift pattern, normal to high and borderline to high. And in the overall exposure here, 20.5 points of change, normal to high and borderline to high -- again, more in the borderline to high shift group.

Moving from these to prolactin, as had been mentioned by our other sponsors -- of course this is important in antipsychotic medication -- we see, and is reflected in our label, from our placebo-controlled databases, 47 percent of olanzapine-treated patients having a change of elevated prolactin, 7 percent in placebo.

Potentially associated clinical events, 3 of 168 for galactorrhea, and gynecomastia, 7 of 286.

We did look, in the placebo-controlled database, and then followed on in the open exposure, with the change in prolactin levels over time. And you can see, represented here, both in males and females, that at week 6, there's definitely an increase in prolactin levels. That tends to go back down as people are followed for a longer period of time.

Moving from that to hepatic analytes, in our treatment-emergent database, looking for abnormal values at any time, ALT moving across a threshold of three times the upper limit of normal. You see that occurring in 12 percent of olanzapine patients versus 2 percent with placebo. Total bilirubin, on the other hand, is changing more in the placebo group than the olanzapine group.

One important way to characterize this data is, of course, Hy's Rule. We actually have a fairly conservative interpretation of that here.

It's often thought of as three times the upper limit of normal, and a total bilirubin shift of more than two upper limit of normal. We went down to 1.5. But, with that, there weren't shifts into Hy's Rule in either group.

Also looked at analytes over time. And here you see ALT, AST and GGT. You see a pattern that's somewhat similar to what you were seeing with prolactin where now you can see week 2 and week 6, showing an increase, and the values falling, as people are followed up over time. Bilirubin, you really don't see much time over time.

Extrapyramidal symptoms. Of course, also, as has been mentioned, very important when dealing with antipsychotic medications. And here -- we actually, of course, rated in our trials for dyskinesia, akathisia and Parkinsonism, using standard rating scales. And there were no statistically significant difference between olanzapine and placebo-treated adolescents in incidence as measured by these scales, and also,

importantly, for olanzapine-treated cases where there was EPS, it was almost always rated mild, occasionally rated moderate, never more than that.

Treatment-emergent extrapyramidal symptoms. This looks at it in a little more detail from our adolescent submission database -- again, looking at the reports now. We talked about the ratings on the last one for reports -- akathisia, dyskinesia, dystonia, Parkinsonism. Again, you can see not really a separation between olanzapine and placebo. With overall exposure, you see the highest individual rate being Parkinsonism symptoms.

QTc prolongation -- also an important issue now with psychoactive medications. And looking at the normal and probably best correction coefficient for QTc in this population, you see, again with placebo-control, not really a separation between olanzapine and placebo. And in the overall exposure database, the 3 percent of cases with a greater than 30-millisecond increase, and no case going over 450.

So to sum up about safety, there are warnings now in our label, and we feel these are very appropriate for hyperglycemia, hyperlipidemia, weight gain, hyperprolactinemia and, in adolescents also, as well as adults -- but we're seeing it a little more -- some of these things -- in adolescents. We also see sedation, transaminase elevation. And feel that all of these things need to be areas of concern and specific reasons for monitoring people who are on olanzapine therapy.

I'm going to move from safety now to our risk management plan. Lilly has a well-established global risk management plan for olanzapine. It includes three basic components. The first component is the safety profile. And essentially you just saw and heard the safety profile. I've just reviewed this with you. The second component is risk assessment. And the third is risk minimization.

I'll present our current and our planned efforts for risk minimization and assessment,

including our REMS for olanzapine. REMS stands for risk evaluation and mitigation strategy. It's a relatively new tool that the FDA can use now to help sponsors identify key goals for risk minimization, as well as methods to evaluate the effectiveness of risk minimization efforts.

Lilly has a REMS in place for olanzapine, and we'll discuss how that will be expanded if these indications are approved.

In our 2006 submission for adolescent indications, Lilly included a plan for risk assessment that was going to conduct a retrospective cohort study to help estimate and compare the incidence of diabetes and dyslipidemia in adolescents with schizophrenia or bipolar disorder versus the general population. At that time, not a lot was known about this.

Well, since then, the study has been completed and submitted for publication, and Lilly investigators did find that both schizophrenia and bipolar disorder seemed to be a risk factor for developing diabetes and dyslipidemia, and also

antipsychotic use. So the risk is there.

Also, in addition to this, Lilly has a standard surveillance program and targeted surveillance for adverse events related to olanzapine. All the potential risks I discussed today for adults and adolescents are included in these targeted surveillance efforts. And they're included in our periodic safety reports to our regulatory agencies and the FDA. We'll, of course, continue these efforts, whether there is approval for these indications or not. And our global product safety group regularly monitors adverse event reports that come to Lilly, and also monitors the FDA AERS database for potential safety signals. We review the literature, and all those things also get put into our periodic safety updates.

In addition, Lilly proposes to conduct a one-year study in adolescents to further evaluate the long-term safety of olanzapine in schizophrenia and bipolar mania in adolescents. This open-label safety study will look at

behavioral weight interventions to evaluate if an intense intervention program is superior to a standard program in mitigation of weight in adolescents, as well as look at safety parameters for olanzapine long-term in these populations. We plan to begin enrollment in this study later this year.

Now, in reviewing Lilly's risk minimization efforts, labeling is the cornerstone of these efforts. Our current approved label includes safety information for adults and adolescents regarding metabolic changes, elevations in hepatic enzymes, elevations in prolactin, as well as sedation events. If adolescent indications are approved, we'll update these sections of the label as we've indicated here on the slide.

And specifically a number of text areas will change that we think will actually give clinicians much more information to evaluate appropriate use of olanzapine in adolescents.

We'll also employ this REMS, this

relatively new tool. REMS have specific goals. Lilly's REMS for olanzapine went into effect March 19th this year. The goal of this REMS is to inform patients of the serious risks associated with the use of Zyprexa (olanzapine) oral tablets, including the risks of hyperglycemia, hyperlipidemia and weight gain.

With adolescent approval, the overall goal with remain the same. So you know the goal. But the tools we'll use to achieve this goal include a medication guide for patients and a communication plan.

The medication guide is a short document written for patients that describes the potential risk of a drug in detail. The patient receives the medication guide when they fill or refill a prescription. It's attached to our product label. Our current medication guide focuses on metabolic changes and includes information about adolescents. And it will be updated.

Our second REMS tool is our communication plan. On approval, the product label, including

the med guide, will be updated within 24 hours and posted the Zyprexa website. In addition, we plan to distribute a "Dear Healthcare Professional" or so-called "Dear Doctor" letter. The purpose of the letter is to inform physicians who are likely to prescribe Zyprexa in adolescents for schizophrenia or bipolar mania about the risks and benefits of the indications. It will emphasize the need to consider other treatments first. This information will also be in our toll-free call center.

We're periodically going to assess the ability of these tools to determine if we're actually meeting the goals of the REMS. If we're not meeting the goal, we'll modify the tools to increase the probability of meeting these objectives.

Assessments will be made at 18 months, three years and seven years after approval. We'll assess the efficacy of the medication guide in a way that we've already done. In getting the medication guide out to adults, we assessed the

efficacy of adult patients with schizophrenia and bipolar disorder in understanding and being able to access information in the guide. We'll perform similar testing in adolescents.

If the results indicate adolescents or their caregivers don't understand the information being communicated, we'll work with the agency to modify the guide to ensure this understanding.

We'll also assess the effectiveness of the communication plan. We'll perform knowledge checks with physicians after the introductory HCP letter has been delivered. As with user testing with the medication guide, if there's a significant lack of understanding, we'll work with physicians and the FDA to improve this communication.

In the periodic assessment reports, we will also report how well Lilly has provided the medication guide to third parties who will ultimately distribute it to patients.

REMS are new to the industry. We'll monitor, we'll adopt the best strategies we can to

meet the goal of the REMS. We welcome input and suggestions from the committee about the best ways to evaluate the effectiveness of these tools.

I'd now like to turn the podium back over to Dr. Robert Baker, who will conclude our presentation with our risk assessment plan -- risk/benefit plan.

DR. BAKER: Hi again. I'm going to conclude with a few comments about benefit-to-risk because, after all, ultimately, the decision about approval or not would be predicated on concluding that there is a positive benefit/risk for the target population.

I think in the case of olanzapine it's most appropriate to start this conversation by talking about risk. In some respects, the news isn't so bad. If you take extrapyramidal adverse events, which are a risk of olanzapine relative to other antipsychotic choices, the results look pretty good. But you also saw a number of adverse events where what we encountered in the adolescent population is greater than you might expect on

some of the other treatments, or greater than we've seen in adult patients, or both.

Dr. Laughren made the point this morning, and Dr. Conley just repeated, that this information is captured already in the U.S. package insert for olanzapine. The slide summarizes that in our warnings and precautions are statements including information -- data on adolescent studies regarding weight gain, hyperlipidemia, hyperglycemia, hyperprolactinemia. In other sections there's information on sedation and hepatic changes.

But irrespective, some of these adverse events are prominent, and we know that you would expect that for -- if adolescent patients stay on over the long term, most of them, 90 percent or so, are going to encounter significant weight gain. That could be a significant hurdle, as you're thinking about, is benefit/risk positive? Unless that hurdle would be overcome by effective risk mitigation or benefits, or a patient population for whom the needed efficacy is the

determinative factor.

All three of these are applicable to our thinking about olanzapine for adolescents, and let's start with risk mitigation.

Rob Conley walked through the details of the risk evaluation and mitigation strategy, but let me stay at a high level by saying that, for olanzapine, as I think is the case for most medicines -- not all medicines, but for most of them, the centerpiece of the risk mitigation is knowledge about its risks and appropriate action by clinicians who are using the medicines.

In the case of olanzapine, there's a lot of knowledge that can influence clinical decisions. We have extensive study in adult patients, 12 years of clinical naturalistic exposure since approval, and this morning you heard about specific results from adolescent research that can inform treatment decisions.

If clinicians are informed, they would, of course, be thinking about these risks in making treatment decisions and recognizing that, in many

cases, the important consideration is not even so much the immediate mortality, but the impact on risk factors that could come to bear over longer-term treatment. Those risk factors are generally identifiable. Weight can be measured. Blood lipid changes can be assessed through laboratory tests. And in many -- not all cases, but in many cases there are actions that can remediate or moderate them. Diet, exercise, medication treatment.

Also, in terms of reversibility, we know that -- well, we know from studies in adults that all of these tend to normalization if medicine is switched away from olanzapine to no treatment or a drug that's not associated with these changes.

Therefore, in terms of treatment selection, this information can inform it -- and more importantly, I think, for the management, can influence a benefit/risk thinking at an individual level that can happen in an ongoing way because, as you think about individual patients, as they're receiving medication, for that individual, you

have a lot of direct information about their own efficacy experience, their own adverse event experience to supplement what you know from the research that we have to provide today.

So out of this, I think that there is some hope that the risk profile can moderated -- there is strong reason to believe it can be moderated through risk management, but obviously the risks cannot be eliminated. They're going to be important considerations, irrespective. So are there benefits to offset them?

That you saw summarized from Dr. Osuntokun this morning, and just to repeat, the efficacy in teenagers with bipolar mania and with schizophrenia was robust and demonstrated in these studies. This is a medicine that, in adult patients, has well-established efficacy and I think is widely viewed in the field as an important choice for severely ill patients, those that don't respond well to other treatments -- tends to be a go-to choice.

You might assume that this could offer

hope for adolescent patients that are in that same situation, if there are those patients.

Many of you are the experts, but we've heard this morning from you. We've heard from other experts with other sponsors that juvenile onset of schizophrenia or bipolar mania, two of our toughest diseases, are associated with particularly tough-to-treat features, bad outcomes across a number of critical parameters about life functioning, life enjoyment or life itself.

Some of those bad outcomes are reflected in the developmental stages because this is a critical time -- it was for all of us in our lives -- in terms of development, but I think that those features make it all the harder to deal with when you have these serious mental illnesses superimposed.

And as you've heard, many patients don't respond to the first, or any given treatment. So for these particular individuals, if there are individuals for whom another option could mean better efficacy, it could mean, for those

individuals, the difference between thinking clearly or not so clearly, or having a positive quality of life or moving forward or moving backwards, being at home, being in the hospital. Those are the sorts of differences that an option -- any option, not just this one -- that would bring better efficacy could change for those patients. And I would ask you to think about those patients as you deliberate the role of this medicine, and really all of these choices today.

So as I mentioned -- my last slide -- I had mentioned to think about those patients, but let's talk about olanzapine in particular. It's a strong medicine. We found that in these teenage patients. There are common and prominent adverse events that would mean that, for many patients, it's not the optimal choice, or first choice. We also found efficacy in these studies that would make us expect that, for those individuals who have the key needs, for whom the urgency of the illness, the poor response to their illness is the dominant of treatment choice -- that, for them,

olanzapine would offset -- the benefit, potential benefit would offset the likely risks of treatment.

We have, as I mentioned -- as I started -- agreed to the FDA's proposal that, if this is approved, the labeling would indicate that it's a second-line choice, and we agree because we think that that would achieve the goals of highlighting, appropriately, to clinicians risk, but also sustaining availability for that subgroup of patients for whom the efficacy benefits might be most particularly relevant.

So let me close with that, and thank you again for this -- and hope that you conclude, as have we, that approval of olanzapine will mean that it's more likely that more patients will achieve the best outcome that's appropriate for their needs as individuals.

Thank you.

DR. GOODMAN: And I wish to thank you, Dr. Baker, and your colleagues at Lilly for a series of clear and informative presentations. We

have about 20 minutes of clarifying questions I would like to do, aim for doing the open public hearings at 3:00 p.m. So that would still give us an opportunity for about a 15-minute break.

So I'm going to -- this is our opportunity to ask these clarifying questions. I'd like to start off with my own, and I want to address to this to both the FDA and the sponsor. As I understand it, your proposed labeling is for a second-line treatment in adolescents with bipolar disorder or schizophrenia.

We have some discussion at a previous FDA hearing about what is meant by second-line treatment, but I'd like to understand a little bit more about the implications. I wonder whether FDA or the sponsor could help us define what is meant by that and how it would be operationalized.

DR. BAKER: Should I go first or would you like to --

DR. GOODMAN: Let Tom Laughren...

DR. LAUGHREN: We actually have a precedent for what we intended in this situation,

and that's the drug ziprasidone. Because of the fairly prominent QT findings, the labeling for ziprasidone basically indicates to the clinician that they should think about other options first. So that's one meaning, and that's really what we would intend to hear.

Another way of thinking about second-line status is a drug like clozapine where the company has actually done a study to show that clozapine works in a setting where other drugs have failed, and so -- you know, that's another approach to thinking about second-line status. That's not what is intended here. This drug has not been studied in treatment refractory patients. But for all the reasons that have been laid out, it seems clear that clinicians should probably think of other drugs first.

DR. BAKER: And -- thank you for that, and we would agree with that, that this study was in all comers. But the results of the study would suggest that while benefits are available, there are prominent risks that would make you want to

think about other routes to achieving those benefits that would pose, in general, less of those risks, but have it available for those that -- that the other choices are not appropriate, for one reason or another.

DR. GOODMAN: Dr. Temple.

DR. TEMPLE: The discussion is sort of indications the gradations of second-lineness that we're talking about. If we're really scared of a side effect of a drug, clozapine, 1-1/2 rate of agranulocytosis, we may well ask for a definitive showing that it really does work in people who fail to respond to other drugs.

The only way you can do that, in my opinion anyway, is to randomize back to the failed drug and to the new drug -- an extremely unusual study design -- it's been done for clozapine and a couple of other drugs -- where the reasons, as I think tom explained well, are subtler than that. It's not that -- I mean, weight gain, after all, is monitorable. You don't suddenly gain 50 pounds without anybody noticing.

We're trying to convey here that, given the variability of responses, it's reasonable to start with something else first, but we don't necessarily insist on that definitive study; that is, a study in failures where you randomize back to the failed drug and the new drug.

And it's an interesting question which we wrestle with all the time: Just how strong does the proof have to be that it really does work in non-responders to other drugs?

Anyway, I think that's part of -- that's been part of our reasoning.

DR. GOODMAN: Dr. Baker, do you have the data in adults that olanzapine would be effective in cases where other -- what might be considered other first-line in the adolescents -- antipsychotics fail?

DR. BAKER: I'll ask Dr. Conley to speak a little bit to information that's available from the CATIE study, and whilst he's coming up, I'll also mention that we have a recently completed trial that is partway along the path to that. It

wasn't a traditional very refractory sort of patients, but we prospectively treated patients with risperidone, and those who had no responded to initial treatment, which was fairly brief, about two weeks, were then randomized to remain on risperidone or switch to olanzapine, and we saw significantly more improvement amongst those that went onto olanzapine.

That's in route to being published, I believe.

DR. CONLEY: Thank you, Dr. Baker. Again, Rob Conley from Lilly. And, yes, in the CATIE trial, which was really more of an effectiveness study, actually, than an efficacy study, because what was looked at is time on drug, olanzapine did have longer time on drug than many of the common comparators. You can see that on this slide -- here we are -- where you see the olanzapine line is the top line, and a longer time on drug for it, compared to quetiapine, risperidone, perphenazine and ziprasidone.

The ziprasidone was not a significant

difference. It was a smaller cell size because of study design issues.

Also, in looking at all-cause discontinuation, when people had failed their first therapy, in the so-called CATIE 2 design -- and this was also just recently published -- now the patients could get clinical, olanzapine, risperidone or quetiapine. And you can see clozapine has done the best. Olanzapine has also significantly separated from the other treatments.

And so there are evidence in adult effectiveness studies that are there.

There's also been recent meta-analytic approaches to the overall clinical trial data in adults, one recently published by John Davis and colleagues and another by Stefan Leutch and colleagues, that looked at overall clinical trial and published trial data, suggesting that olanzapine had, overall, more effectiveness than other antipsychotics.

So in the adult literature, this is reasonably well-known.

DR. GOODMAN: Dr. Twyman?

DR. TWYMAN: I think this is for Dr. Conley. Given that the signal strength appears to be stronger in the adolescent population versus the adults for some of these safety signals, have you had a chance to look at this adolescent population to see if there are any potentially predictive markers or characteristics that can help guide practice?

And if those markers could be identified -- this is a question for the FDA -- what would it take to be able to have that in the guide -- at least in the labeling aspects to guide practice?

DR. BAKER: I can speak to that a little bit. The biggest difference we see is more vulnerability to weight increase among adolescent patients. We've looked for explanations within the adolescents. We've also looked because, although it's not quite as great an amount, it's clearly the major adverse event concern, or one of the major adverse event concerns with olanzapine

in adults. So in our much larger data set there, we've explored whether we could have a marker.

We've done pharmacogenomic studies, have done quite a bit of work on that, without yielding something that would be predictive in terms of a blood test.

We've done post-treatment studies, among adults -- and this was confirmed in adolescents -- that indicate that once somebody is on the medicine, the rate of weight increase during initial weeks is very predictive of whether they're going to end up in the greatest categories or not. So that's the sense in which monitoring can be very informative.

We've also looked at pre-treatment predictors where, again, we have much more data in the adults to predict. Some of this has been done outside of Lilly. John Davis, for example, has looked at it, and he's found four predictors that seem to discern. And I would think that all four of these might have something to do with why we're seeing more in adolescents.

The first is that treatment-naive patients have a considerably greater increase than those that aren't naive. It might just make sense that, in some ways, any medicines, even traditional antipsychotics, are probably associated with some weight gain, and as one climbs that curve, then those that are more associated may take you further up that curve. But if you haven't started there, it's a bigger gradient.

Second is, amongst adults, younger people have less weight gain. And, in fact, at the geriatric end of the spectrum, there tends to be much less weight gain. And so it's not surprising that we see that trend extending to a younger age group.

Thirdly is that BMI is predictive. Those that are most thin coming in -- and at least speaking for myself, I was thinner when I was younger -- tend to gain more weight over time, so we might see that as a factor in adolescents.

And then, finally, smoking status.

Non-smokers gain more weight than smokers, and at least in our trials, we found lower rates of smoking in the younger patients.

DR. GOODMAN: Thank you.

Dr. Grady?

DR. GRADY-WELIKY: I had a question regarding the response differential between the Russian and U.S. cohorts, and I appreciate the remark about there being perhaps a greater placebo response here in the U.S.

I was wondering, first, if you could share more specific data about the placebo response, and then, second, if there was any information about whether or not the patients in Russia were more medication-naive or were our patients somehow more complex -- but I am very puzzled by that response differential.

DR. BAKER: I'll ask Dr. Osuntokun to answer those specific questions you asked, but before he does that, let me speak to the general question of being puzzled because we, as well, were puzzled. And conducting studies across many

countries -- we often do -- and invariably you'll see greater response in one than another.

In this case, we saw more of a gradient than we would normally expect to see and, therefore, our investigations were targeted toward, is this something real that would distinguish outcomes in Russian individuals versus American individuals, or is it a matter of chance?

He's looked at a number of those, including the ones that you've asked about.

DR. OSUNTOKUN: Thank you for the question. In an attempt to further understand the possible explanation for these differences, we've looked at the following that we present here on this slide, if there were differences in baseline characteristics. We did find that there were some parameters with statistical differences, comparing the two countries. And those, when applied to a model, with those as variables, we don't see -- or I should say we saw a consistent finding with those variables in that the overall results were consistent. The olanzapine group separated from

placebo in the -- in the overall patient population. Still, those in Russia had a greater improvement, and we saw less in the U.S. population.

We looked at secondary efficacy measures. Perhaps there will be some discrepancy in the way one scale captures symptom changes. Those, again, were very consistent with the primary findings.

Going down the list, as you see, disposition, for instance, looking at if we saw a consistency in lack of efficacy as a reason for discontinuation. In fact, in both the U.S. and in Russia we saw a statistical difference in that those on placebo had higher rates of discontinuation due to reasons related to efficacy, consistent with the overall treatment population.

Response rates were consistent with the primary findings, numerically advantageous in those on olanzapine, but did not show statistical differences, which was similar to what we saw in the primary outcome.

Differences in dose was another consideration. The mean daily dose in the U.S. was actually just slightly higher than what was seen in the Russian population, 13 milligrams compared to -- I believe it was 11 milligrams in the Russian population.

We looked at the influence of concomitant medications. Perhaps there's a difference in how, for instance, benzodiazepines, or rescue benzodiazepines are used. Interestingly enough, there was actually a higher placebo to olanzapine rate of use of benzodiazepines in Russia compared to the United States.

Weight gain, we saw the same pattern of statistically greater changes in olanzapine compared to placebo, although you could clearly see that there were weight differences from baseline, perhaps due to some other reasons.

We looked at a specific population that had unusual high placebo response in both countries, trying to understand if there were any specific reasons that we could discern. This was

challenging because you had to go back and try and get investigator comments or look at comments from the case report forms. We didn't see anything consistent that would explain clearly why we saw this disparate placebo response.

DR. BAKER: How about the question on treatment-naive --

DR. OSUNTOKUN: Yes. Perhaps while our group is looking for the slide, I would say in the -- there were 23 patients -- so what this slide shows is a breakdown by country, Russia versus U.S. Actually -- yes, this shows those who had had at least one previous treatment, essentially those that were non-naive.

What we see here is a similar number of patients who had had -- or who were perhaps non-naive in the U.S., compared to Russia.

When we did look at the group that were naive -- actually, most of them were in the United States -- I believe it was 23 overall, with about 17 from the United States -- and, actually, most of those were, I believe, on placebo.

DR. BAKER: Thank you, Wale.

So if I can add to that, you know, ultimately we have the one study, so it is going to be a judgment call, but our conclusion was that the efficacy is bona fide, and that would be based partly on the fact that though we saw a much bigger placebo response directionally, it was still a positive effect size in the U.S. The secondary outcome of treatments due to lack of efficacy was very strongly differentiating from placebo in the U.S.

And then, ultimately, you rely on what you know about this medication for treatment of schizophrenia in adults, which is very well-established.

DR. GOODMAN: Dr. Vitiello?

DR. VITIELLO: You mentioned you envision a one-year open-label naturalistic follow-up. How big that sample would be -- that will include both schizophrenia and bipolar?

And question number 2. Wasn't there a similar study -- I think it was done in Germany --

that your company funded? And, if so, was there any useful information that came from that work?

DR. BAKER: Wale, do you want to address the details? The sample include both schizophrenia and bipolar patient -- the question is, how large is the study?

DR. OSUNTOKUN: This is the one-year open-label study we propose to conduct. I believe the sample size is looking at 200 patients in total, and it's not -- there aren't going to be specific guidances in terms of what diagnostic category fractions of patients can belong to. Basically, we are planning to enroll patients with either of the two diagnoses into that study.

DR. BAKER: And I'm not personally familiar with the German study that you've mentioned, and I don't see any nods from over here, but we can look into that.

DR. VITIELLO: Yeah. It was a publication. I think it was Dr. Ditmann that I think is with Eli Lilly in Germany.

DR. BAKER: Yes. That would be Ralph

Ditmann. A.J. Do you know the study? If not, we can look into it and get back to you.

This is Dr. Allen, who is a child psychiatrist working with Lilly.

DR. ALLEN: Yeah. The study was LOAY, and it was a study that was conducted in Germany. I'm sorry. I missed the point of your question regarding that in terms of -- that was schizophrenia patients, if I remember correctly.

DR. VITIELLO: Yeah. I mean, since you would like to do a follow-up, open-label follow-up for 52 weeks in the U.S., I wonder if you have some useful information that came from that study.

DR. ALLEN: That study would have, I believe, been included in our safety analysis, and so the FDA already has access to that, I believe. And there's still the feeling that we need to do some additional work on this, which is why we're proposing the additional study.

DR. GOODMAN: Dr. Day?

DR. DAY: I wanted to comment further on U.S. versus Russia -- and this is a gentle

question, and that is, once we look at all of the medical and trial features of the studies, is there a possibility that there are social and cultural differences that could be at play here, and economic as well? So being able to have your medications for a desperate situation with a child free during a study could have some effect. And you may have some of the data already collected about the socioeconomic level of the people in all the studies, and there are some standard measures for all this, and that might be something going on, and I'd like your comment on that.

And one other thing, and that is, in the whole society, the effect of direct-to-consumer advertising of prescription drugs can enhance the thought or the belief that drugs are good and help -- might have an effect on placebo, and if so, a good country to then do these kinds of trials on might be New Zealand since it's the only other country in the world that currently allows direct-to-consumer advertising of prescription drugs.

DR. BAKER: Thank you for that question. I have a couple of comments that might be relevant. First, to the broader question of direct-to-consumer advertising, that I don't have -- it's an interesting hypothesis, whether the placebo response here is stimulated by what people see on television. I don't have direct information. Certainly in this case, although it's not what you're asking, we would not be intending any direct-to-consumer television advertising.

Two things about the Russian sites, we have had Russia as a country in other schizophrenia studies for olanzapine and other antipsychotic drugs. We've gone back to look at whether this is something that we see systematically, and it's not. We do see different countries coming out ahead from one study to another. We don't see it systematically.

But we do see systematically something that I think might fit with what you're suggesting, which is that those studies where each

investigator is able to enroll a large block of patients, sort of get into the study, fill all the cells within our randomization, are more likely to yield a clean answer, distinguishing between treatments. And in this particular study, that was the case. There were fewer sites in Russia than there were in the U.S., and that does tend to be associated with treatment outcome.

I don't think that we have the socio demographic data convenient that you've asked for. What we do know is that more of those subjects in Russia were hospitalized during the course of treatment than in the U.S. We don't have a strong hypothesis for why it should affect it, but that was the case.

DR. GOODMAN: Dr. Gogtay -- oh, Dr. Day, do you want to follow up?

DR. DAY: Just one comment. The comment about DTC wasn't particularly for this product.

DR. BAKER: I understand.

DR. DAY: But in general. And I just want to make one other from, from Dr. Conley -- I

know that he knows this, but just for the assembled multitudes here. It is true the REMS is relatively new, has gone into effect, but there was a previous system called a risk map, and before that, risk management plan and so on, and many of the elements have been around for some time, from the "Dear Healthcare Professional" letter, medication guide and so on.

It is a new configuration of those things, and it's good to see that the sponsor has already done quite a bit in terms of now what we call REMS, and has other proposals ready to go if it is approved.

DR. GOODMAN: Dr. Gogtay?

DR. GOGTAY: I had one more follow-up question about the U.S. and Russia differences. One of the things that's noticeable is the effect size for the Russian group in the outcomes measures is .93 while, for the U.S., it's .3, which is a whopping difference between the two.

I have a question at a more concrete level, so if you just focused on the U.S.

population, do any of the effects survive in terms of the outcome measures? Because the slide that you showed, as a follow-up slide, if I am not mistaken, the U.S. population did not show any more significant P-value.

DR. BAKER: Yes. This -- let me take this opportunity to correct one thing that I just said to Dr. Day, because my group had sent me information up here. I said more hospitalization in Russia. It was the reverse. It was actually more of the Americans were in hospital coming into study, but we therefore thought, you know, did that mean more opportunity for treatment might make a difference.

Let me show the slide that you're alluding to in terms of differences for effect size. We saw larger drug-placebo difference in Russia than in the U.S., driven primarily by a bigger placebo response in the U.S.

The study was not powered to look at the U.S. alone, but on this primary outcome -- it had not been intended to do it, but on this primary

outcome, if we had had U.S. alone, there would not have been a significant separation.

In terms of the secondary measures, as I mentioned, one we think very transparent one is the likelihood of patients discontinuing due to lack of efficacy, and -- I don't have a slide for it, but I could tell you that that was -- and I think it's mentioned in the briefing document -- it was significantly greater among placebo-treated patients, more discontinuations for lack of efficacy than among olanzapine patients. I have the slide now.

So you still see a bit of a differential between the U.S. and Russia, but in this particular measure, in U.S., the secondary outcome did survive, even within the smaller U.S. subgroup.

DR. GOGTAY: If I could have a quick follow-up. One other question related to that is some of your baseline measures were statistically different; for instance, the number of episodes of depression or manic episodes. If you adjust for

those differences, do any of these outcome measures survive?

DR. BAKER: It looks like Wale will speak to this. I assume that this is relevant -- this U.S.-Russia difference was in the schizophrenia study and not in the bipolar study.

DR. OSUNTOKUN: Right. That is correct. What you refer to is in the bipolar study where some baseline characteristics were different, such as previous number of manic episodes, previous number of depression -- and even the CGI bipolar depression, when those were adjusted, it did not make any difference with the overall study results in terms of YMRS changes from baseline to end point.

DR. GOODMAN: One more.

DR. GOGTAY: I do have an unrelated question to the weight gain and metabolic changes. Again, the adverse events are fairly striking, and I know you've reported that they're also there in the adults. Just to put it in perspective, can you give us some quantitative idea about how much

worse are they in adolescents, or if at all, what is the long-term outlook, for instance, in terms of -- even if you take weight gain, do kinds continue to gain weight forever? Or, for instance, what is it compared to the other atypicals? If you can put it in the context.

DR. BAKER: Yes, we would have information on any of those questions. We have some, for example, that show the course of weight gain over time in adolescents versus adults.

Yes, first in terms of general magnitude, we reported to you what is the weight gain among those patients who stay on the drug for a long time. More traditional approach, as you'd see in many labels, would be, what's the average weight gain over long term, including those that drop out early? And that would be a benchmark where we could compare between them.

So for adult patients, we see that average of about 5 kilograms versus about 7-1/2 kilograms among adolescent patients.

To the question of what happens over the

long term, what we do see in adult patients is that the weight gain is sharpest in the first month of treatment, and in fact, how sharply it goes up during that time -- here we go. How sharply it goes in that time, at the individual level, is predictive of who will gain the most.

In adult patients, we see that that tends to flatten out, and it especially flattens out after about eight or nine months of treatment, which is longer than the treatment that we have in adolescents. So we don't actually know what happens beyond about eight months, because that's as far as we've gone.

But this would be a demonstration out to -- it looks like 24 weeks, showing -- this is an observed case analysis, so it's excluding from it dropouts. You might worry about who's dropping due to weight gain, but actually we find that if you include those in the analysis, if you include dropouts in the analysis, you have less weight gain. So by looking at the observed cases is how we see the worst case among our analytic

approaches.

And here's the pattern you see. It's leveling off. We've not gotten to a point among adolescents where it is flat. Other sponsors have made the comment that some of that might still be normal growth in adolescents at the far end. At least 80 percent of what we're seeing up to that time is not normal growth; it's a drug effect.

DR. GOODMAN: Given the spirited discussion that was stimulated by the Russian question, I'm going to revise our timetable slightly. Let's give ourselves another five minutes for questions. We'll take a 15-minute break after that, and start the open public hearing at 3:15.

So I will allow about four or five more questions. Dr. Caplan first.

DR. CAPLAN: I had a question about the diagnostic criteria for the schizophrenia project. The three criteria that were put up were hallucinations, delusions and peculiar fantasies. And it's not so clear to me why peculiar fantasies

are separated from delusions.

And then if we want to also address cultural issues, definitely between studies in the United States and Russia, how do we define -- you know, there might be significant cultural differences in what is called peculiar fantasies in these different countries. So I was just concerned about the diagnostic reliability and the criteria.

And why wasn't thought disorder included in the criteria, which is typically one of the DSM criteria?

DR. BAKER: So let me first clarify that DSM criteria and confirmation with the Kiddie SADS of meeting the DSM criteria were required to enter the study.

In addition to having to meet those diagnostic criteria, individuals had to meet a baseline symptom severity criterion, and that criterion focused on these three particular ratings, or terms, within the BPRS for children which we use. So this was -- these were not the

diagnostic criteria. These were supplements for patient's severity criteria to getting in.

You have a broader question about diagnostic differences, I guess, between U.S. and Russia, and I'm not sure that we have an answer on that question.

A.J., do you have thoughts on that?

DR. ALLEN: A.J. Allen, child psychiatrist at Lilly. I think one of the contexts here that you might keep in mind is these are -- patients are being treated by clinicians who are from the same culture and, therefore, they're going to be judging the peculiar fantasies, for example, based on what would be peculiar to them within that culture.

Now, granted, it's hard to make comparisons between the U.S. and Russia in what you might consider peculiar, but within the context of what's available within the DSM, you're going to have cultural sensitivity because of who's doing the treatment and diagnosis.

DR. GOODMAN: Dr. Towbin?

DR. TOWBIN: Thank you. Actually, I have a question that is for Dr. Baker, but also Dr. Vitiello may wish to make a comment.

Earlier today we heard about the TEOSS study, and I believe that olanzapine was one of the drugs that children could be randomized to in the TEOSS study. I think we're all in agreement that the metabolic profile of olanzapine makes it stand out as a more concerning drug, and that's why this second choice option has been offered. But you've suggested that it may be more effective. And so this TEOSS study gives us a unique opportunity to look at how this drug compared to two others in sort of a head-to-head trial, and I was wondering if you could comment on that.

DR. BAKER: Sure. Well, let me start by acknowledging that it did not look more effective in the TEOSS study. It was a small study, but olanzapine did not stand out in that study, so our comments are that, in our studies versus placebo, we found that it's effective; therefore,

potentially and effective choice. And then extrapolating somewhat from adults where we have many more studies and a lot to draw on, we would have reason for hope.

This particular TEOSS study, though, would by no means support a differential superiority across all the randomized patients.

DR. GOODMAN: Dr. Vitiello?

DR. VITIELLO: Yes, I agree. I mean, the TEOSS study is too small to talk about differences in outcome. It picked up some differences, certainly, in metabolic side effects so that olanzapine clearly had more weight gain and other changes in metabolic parameters than the other drugs, but it doesn't settle the issue if olanzapine may have superiority over the other. It doesn't really provide any evidence, but absence of evidence is not evidence of absence, so...

DR. GOODMAN: I will let our two cardiologists have the last word.

You had another word, too, Dr. Towbin?

DR. TOWBIN: I just had a quick question for Dr. Osuntokun related to the diagnostic criteria for bipolar disorder, coming back to an earlier comment. He had said that these individuals had reckless behavior, racing thoughts, agitation and distractibility. And I was wondering how, in your study, you differentiated individuals who had chronic symptoms of those -- that is, chronic appearance of those symptoms from individuals who had acute mania.

DR. OSUNTOKUN: My description of those symptoms was really drawing from my own personal experience and from what we've heard from the clinical experts in terms of how patients with prominent symptoms may present.

I don't believe we've looked specifically at -- that is, the patients in our study, if we had those who had more acute symptoms or chronic symptoms. The criteria was that they had to have met the criteria for an acute episode, or a current episode, of either mania or mixed symptoms

at the start of the study.

That could have been their first presentation, or it could have been someone who had been diagnosed previously who, at that point in the study, was also meeting the acute criteria.

DR. GOODMAN: Dr. Granger?

DR. BAKER: Could I just add one -- sorry. Could I just add one thought? Because this question has come up several times today, and I think it's an important one. In these research studies, we do have Kiddie SADS to verify the diagnoses, but in clinical practice, you often wouldn't have that. And I do think, as we think about risk management, it might be an important consideration because, after all, part of that communication is that it's only for a certain population that the benefit/risk is positive.

We do have clues, I think, in the adult population -- at least in my view -- would be applicable. Here -- DSM tells us that if it's only irritability and not elated mood, that you look for more of the supporting criteria.

We all know that if a patient has had the typical cyclicity, that you're going to feel stronger in the strength of your diagnosis than not, and it's possible we could think about some way of communicating that with the other communications -- across companies, really.

DR. GOODMAN: Thank you for your patience. Dr. Pritchett.

DR. PRITCHETT: I want to talk about the vital signs for just a minute. If you look at Dr. Conley's slide number 65, there's a bullet at the bottom that you didn't mention that talks about the heart rate changes, plus 6.3 beats per minute, minus 5.1 beats per minute for placebo, so that's a difference of 11, a placebo-adjusted change from baseline of 11 beats a minute.

Page 136, section 5.11 of your briefing document says there were statistically significant increases for supine systolic blood pressure, standing systolic blood pressure, supine diastolic blood pressure, standing diastolic blood pressure, supine pulse and standing pulse. Every vital sign

you measured increased.

What was the magnitude of those changes? The briefing book doesn't tell us.

DR. BAKER: I've put those on the screen.

DR. PRITCHETT: Okay. Thank you.

DR. BAKER: And while you're looking at that, I'll comment that we did see a bigger pulse increase across our adult studies. On average, we see an increase of about 2 beats per minute versus 6.3 here.

DR. PRITCHETT: Could you just print that out or send it to me as an e-mail? Let me --

DR. BAKER: I think we can get a printout --

DR. PRITCHETT: -- think about it overnight.

DR. BAKER: -- and hand it to you, yes.

DR. GOODMAN: Dr. Granger, did you have a question?

DR. GRANGER: Yeah. I'd just like to, first of all, congratulate you for doing this one-year study. Can you just tell us a little bit

more about that in terms of the design? Is that randomized to -- what's the design of that?

DR. BAKER: Everybody is on olanzapine, so there's not a randomized comparator.

DR. GRANGER: Right.

DR. BAKER: A primary question, in addition to the naturalistic results that we would see, is how much interventions could make a difference for the weight increase, so what is randomized is whether it's general counseling versus a more specific and intensive program to moderate weight gain.

DR. GRANGER: I mean, I think, from a cardiovascular standpoint, again, this constellation of -- you know, it's like generating the metabolic syndrome in a group of adolescents in a fairly substantial way over a short period of time. And I think it would be very helpful -- maybe you have some information on this. Recognizing that a lot of time these drugs may be used for a short period of time, and therefore maybe it's not going to have such a long-term

effect on cardiovascular health, but do you have a sense about how long it takes to resolve these abnormalities that occur once the drug is discontinued?

DR. BAKER: I have information on several of the points you raised. First, in terms of what is the natural history of people staying on medicines long-term or not, these do tend to be lifelong diseases, especially schizophrenia; bipolar is more episodic. And, therefore, in the ideal state, if there's a medicine that's working well, a person would stay on it for very many years.

In practice, switch rates are very great. NIH conducted an 18-month study where it found that, even on the patients -- the group where patients would stay on the longest, which was olanzapine, still the average was only about half of that time. And, in practice, in tougher patients, like adolescents tend to be, we would expect switches.

In terms of how much -- or how quickly

you would see improvement, we have some clue to that from adult studies where we look at regression and changes in -- excuse me. In the adult studies, we have placebo-controlled maintenance studies in schizophrenia or bipolar disorder where there is a randomized assignment after stabilization to placebo or staying on olanzapine. Those that go on placebo tend to have a pretty sharp increase. I don't think we could claim that it gets completely back to baseline, but just like the weight is going up very quickly, within the first month there's a fairly sharp increase, and lipid parameters tend to improve as well.

Of course we've thought about this in the same way, which is that these are risk factors for cardiovascular or metabolic problems, and how will they play out over time? We've looked at that across clinical trials where we don't see differences, certainly in adolescents, but even in adults, in adverse cardiovascular end points, death or serious cardiovascular events, between

olanzapine and active comparators in adult studies, but you probably wouldn't expect to see that, since those trials are short.

We've looked at it in epidemiology that would speak to the -- what you have in the market currently, just how people are using it. FDA AERS databases give you a window into that. We don't discern from that a clear signal of a difference in cardiovascular outcomes. So, therefore, we think the key consideration would be, what would you expect based on what you know in the general population?

You know that there are Framingham results, so I think that we have less -- from the data we have to date, including real-life observations -- less of a signal of greater rates of cardiovascular events, but more of an expectation, because you would expect that if these changes persist, that you'd have the same outcome in psychiatrically ill patients as in -- as in the general population.

And I'll close by just -- if we can get

one slide, which is the recent CATIE publication on this.

This CATIE study you heard referred to earlier was the NIH's randomized comparison of four atypical antipsychotics, and perphenazine. There's been a recent publication, and in that publication, we -- they, those investigators, applied the Framingham formula, based on what they saw in that 18-month study, to predict what would be the difference in outcome.

And what they found was that for olanzapine, on average, the percent increase of developing coronary heart disease over the next decade would go up by half of 1 percent. Quetiapine also went up by less of a factor, and the other treatments actually went down.

I found most interesting the slide that I'm showing you now, which looks at that based on baseline cardiovascular risk. So you might think of adolescents, of course, of having very low baseline risk. This is based on the baseline laboratories, blood pressure and so forth, going

into it.

If your risk was less than 5 percent of coronary heart disease over the next ten years, olanzapine treatment would be estimated to increase that risk by 1.1 percent. And to orient you, olanzapine is on the left in each of the groups.

In the middle risk category, there's less of a difference. The biggest risk differences were seen in those patients that were at the highest risk to start with, going into the study, and in that case olanzapine -- it improved across all drugs, but the olanzapine improvement was significantly less than the other drugs.

In the CATIE study, these were driven primarily by lipid differences between the treatments.

DR. GOODMAN: We're going to take a -- thank you very much. Appreciate the thorough discussion. We're going to take a 15-minute break. When we resume, we'll be going to the open public hearing portion of the meeting.

(A recess was taken.)

DR. GOODMAN: Welcome back, everyone. I'm going to read a statement regarding the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the

beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way where every participant is listened to carefully, treated with dignity, courtesy and respect.

Therefore, please speak only when recognized by the Chair, and I thank you in advance for your cooperation.

Diem, do you have a comment to make?

DR. NGO: Yeah. We'd just like to remind all the open public hearing speakers that you have four minutes total. The timer will be green when you start, and you have a one-minute warning, yellow light. And at the end of your four minutes, the microphone will cut out.

DR. GOODMAN: Okay. I would like to invite our first public speaker. Is there going to be a slide that identifies them?

Okay. Our first speaker is Marc Peters.

MR. PETERS: I have no financial relationship with any of the parties stated.

My name is Marc Peters, and I currently work as a campus chapter coordinator for Active Minds. We are a nonprofit that works to raise mental health awareness on over 200 college campuses across North America.

I never thought that this is what I would be doing. Four years ago, I could barely envision myself graduating college. That's when my life turned absolutely upside-down, and that's when I had a severe psychotic break. I had been

misdiagnosed as severely depressed in high school and put on antidepressants that exacerbated my actual condition, bipolar disorder. And I was sent into a tailspin.

I heard voices, and I thought I was getting specific guidance from God. I lost completely touch with reality, seeing connections that weren't there. I spoke fast that any lucid individual could not keep pace.

I was admitted to Sheppard Pratt mental health facility in Ellicott City, Maryland, and was kept there for almost a month. It took the doctors nearly that long to find a combination of medicines that would work for me. Because of how far I had spun out of control, there was a real need to slam on the brakes with an antipsychotic drug. I was first given Seroquel in inpatient treatment, and switched to Geodon in outpatient treatment.

I can only speak for myself, but I know that I found Geodon to be terribly crippling. I remember a family friend trying to get me

re-acclimated to the outside world by taking me to see a play, and my thought processes were so stunted that I could not follow the simple plot lines. I was reduced to tears in my frustration, sitting in the theater, rocking back and forth slowly, trying to calm myself, trying to figure out how my life had fallen to pieces so quickly, and being thwarted by the mental blocks induced by the medicine.

My reaction to the medicine and frustration grew so severe that I became suicidal because I felt that life was not worth living under those limited conditions. Thankfully, I did not act on those impulses. I readmitted myself to outpatient treatment so that Sheppard Pratt could oversee my transition off of the medication.

I then forced myself back to college within five months of my original episode. At that point, I had thought I hit rock bottom. I thought spending a month locked in a mental healthcare treatment facility was rock bottom, but I was wrong.

Going back to school was rock bottom. My school did not have a particularly active counseling center. I was limited to three visits a semester, and mental health care in the surrounding community was overburdened and hardly a resource. My school did not have any type of mental health advocacy group. I was stuck going to a DBSA group in the city where I was the youngest member by 20 or 30 years.

Just having a student group like Active Minds, which was meeting weekly and which could provide outreach and information in a peer's voice would have made a considerable difference.

We are not a support group, but members are traditionally open and accepting to students going through very real struggles with mental illness. I can't put into words what a difference it would have made to have a more welcoming environment on my campus.

No matter what side of the debate you come down on with regards to medicating adolescents, we should all be able to agree that

more needs to be done to make these young people feel accepted. I'm proud of the work that we do because more students walk away educated about their options, and more students know that they are not alone in their struggles.

I do not envy your position of having to make such a weighty recommendation that will likely affect the treatment of mentally ill youth in America, but I encourage you, in your debate, not to lose sight of the entire picture, a picture that must include strong outreach and education, in order to prevent the tragedies taking place in communities across our country.

My story turns out okay. I still see a talk therapist and I found a combination of medicines that work for me. It allows me to lead a highly productive life.

I was also incredibly fortunate that I found supportive faculty in college, like the chair of our writing department who taught me to sort through my madness with a pen and a pad.

From a personal perspective, I have no

real qualms with targeted use of these drugs to help young people, and I want everyone in my position to have the same change that I got. However, if you make a decision like this without setting up the proper support system, then you're asking these kids to sink or swim on their own.

Without the necessary structures at secondary schools and universities, you are dooming them to fail, and I don't think we have to settle for that. There is no reason that, with proper support, these youth can't succeed. Thank you.

DR. GOODMAN: Thank you very much.

Dr. Julie Zito

DR. ZITO: Julie Zito. No conflicts with the industries involved.

Thank you, Dr. Armenteros and panel members. I ask the panel to focus for a few minutes on a single question: What regulatory measures are needed to assure appropriate medication use after marketing?

I post this question as an investigator

in psychiatric pharmacoepidemiology. We deal with medication use after marketing when far larger populations are exposed and we can evaluate effectiveness answer safety in real-world patients under usual practice conditions.

Post-marketing data better reflect the health of the public, thereby responding to FDA's mission which states, quote, the FDA is responsible for advancing the public health by helping to make medicines more effective, safer and more affordable.

Yet, FDA spends a great deal of its time and talent devoted to pre-marketing medication assessment where this is neither real-world effectiveness, nor long-term safety data.

This week, Commissioner Hamburg and Deputy Commissioner Sharfstein direct the agency to address medical safety problems by pursuing opportunities to help advance science, quote, even if these opportunities lie outside the realm of the agency's usual routines.

Today the panel has an opportunity to

step outside the realm of the usual regulatory response into post-marketing for the proposed revisions to the existing labels of three antipsychotics. How?

First, the panel should consider recommending conditional approval for the schizophrenia indications because schizophrenia is extremely rare in youth aged 13 to 17. With such a limited target population for the marketing of these medications, increased promotion for this rare labeled indication may have an unintended consequence, namely, to increase antipsychotic use in younger children for the many behavioral conditions that are currently off-label. And we know such use has risen dramatically in community-based youth populations. So there really is a big market in this age group, but not for schizophrenia.

Risk management of long exposures in real-world populations of young schizophrenics can be assured by mandating close monitoring for baseline health status, benefits and adverse drug

events, as a condition of approval. Conditional approval would be lifted after cohort data assures us that the benefit/risk assessment is there for appropriate and safe use as demonstrated in real-world populations.

Second, the panel should consider rejecting approvals for pediatric bipolar disorder because accepting them gives tacit acceptance of a diagnosis that requires further validation.

NIMH Director Insel challenges the credibility of pediatric bipolar disorder and guideline author John McClellan states, quote, characterizing bipolar as frequent, brief, intense outbursts of mood and behavioral dysregulation represents a fundamental change in the definition of the illness with call bipolar disorder.

So severe emotional dysregulation, perhaps; pediatric bipolar disorder, no way.

Thank you for considering these opportunities outside the realm of the agency's usual routines.

DR. GOODMAN: Thank you very much.

Dr. Safer?

DR. SAFER: My name is Dan Safer. I have no conflicts of interest. I'm a child psychiatrist in Baltimore, part-time in private practice. And I see adults as well as children, and I prescribe atypicals, mostly for adults. And I'm particularly concerned about the diagnosis of pediatric bipolar disorder because there's really a lack of agreement among the experts.

If you take a look at the Harvard people, they see it as a chronic disorder, and that irritability is the primary deciding -- or discerning feature. And the people in St. Louis see the disorder as episodic, and the primary features are elation and grandiosity. And then there's the NIMH people, and they see the problem as severe emotional dysregulation. So there's really no agreement.

There's also not agreement in the measures that they use. There's a poster that I included in the handout to the committee that is by Galanter from Columbia, and it looks at all the

measures that are used for pediatric bipolar disorder in children, and the Kiddie SADS is not the only one. There's six other measures, but I can't get into it now because of the time.

There's also a difference in pediatric bipolar in relation to the DSM. The DSM is very specific; that is, for mixed bipolar and for bipolar manic, it requires seven days or more of the symptoms. In pediatric bipolar in the St. Louis and Cleveland and Pittsburgh group, it's a period of at least four hours, and them in comes periodically, like ultradian cycling. So it's not the same as adults.

There's also -- are some medication differences between kids and adults also. That is, there's a recent Depakote study that was done with Depakote ER, and the results were negative -- and it was a very large study. It was 150 kids and 25 sites. And there's a number of recent studies on lithium that were not positive either.

Now I'd like to talk about the Young Mania Rating Scale, and that's a concern because,

if you look at the items, there's 11 items, and four of them are irritability, disruptive behavior, hyperactivity and reactive speech, and they comprise 45 percent of the points on Young Mania Rating Scale, so that you can get a change with atypicals just in terms of behavior.

And if you look at grandiosity, it's -- it's not much at all on the Young Mania Rating Scale in the studies on olanzapine. And also elation wasn't much; it was one of the five lower categories -- the top of the lower five categories -- in terms of change. So the Young Mania Rating Scale is not useful; it shows mostly behavioral change.

So I advise the committee to not approve the indication for bipolar disorder because of the category. And if they want to approve it for an indication, they should approve it for serious behavior disorders or emotional dysregulation. And I think they ought to change the age on the category bipolar because there are very few kids that meet the criteria under age 16 who are

clearly manic on most measures. Thank you.

DR. GOODMAN: Thank you, Dr. Safer.

Dr. Brown?

DR. BROWN: Good afternoon. I'm Dr. Ronald Brown, professor of public health and dean of public health at Temple University. I have no financial conflicts of interest associated with any of these drug companies.

Thank you for the opportunity to address you today on behalf of the American Psychological Association on the matter of new drug applications filed for Geodon, Seroquel and Zyprexa.

Three years ago, I chaired the APA working group on psychotropic medications, which surveyed the complex landscape related to the treatment of childhood mental health disorders. At the time, the working group delineated significant reasons for caution regarding the use of psychotropic medications in children and youth.

Despite advances since 2006 in the knowledge base, the thrust of this important report remains entirely applicable: family and

healthcare providers must act as partners in considering treatment plans to address mental health disorders among children and adolescents, and they must consider the real trade-offs between the psychological benefits and serious risks associated with psychotropic medications.

Today, fundamental concerns persist about the research on the use of psychopharmacological treatments during childhood. First principles for treatment of children and youth are extrapolated from the adult literature, and for many reasons, few randomized controlled trials exist that involve subjects under the age of 18.

Of the few pediatric studies that do exist, many include small sample sizes and attendant methodological weaknesses. Also, ecological valid effectiveness studies often fail to reflect the gains demonstrated in controlled clinical trials.

Finally, adverse side effects and safety issues exist for all drugs examined in the report, and we found a great need for more information on

the long-term benefits, and particularly the long-term risks associated with psychotropic medications used to treat childhood disorders.

The APA working group also specifically examined the literature on childhood bipolar and schizophrenia spectrum disorders and their management. Fortunately, these disorders occur at a very low frequency in the pediatric population, but this fact impedes quick advances in research and treatment. No studies on bipolar or schizophrenia spectrum disorders found in the course of our literature review attempted to address long-term safety and effectiveness issues for children and adolescents.

For bipolar disorders, the working group included in its reviews ten studies on the use of psychopharmacological interventions for children and adolescents. A double-blind, placebo-controlled trial established the efficacy of Seroquel as an adjunct to valproate, but no studies specifically examined the efficacy or safety of Seroquel itself.

Open trials supported the use of Zyprexa, but included no control group and yielded results that our work group labeled "no evidence of effect." We found no studies on Geodon.

The profile looked similar for diagnoses of schizophrenia spectrum. For Zyprexa, we reviewed one randomized baseline controlled trial that yielded results we labeled "no evidence of effect," and additional studies of this drug used no control group and yielded results we labeled "no evidence" or "small evidence" of effect.

Case studies, valuable as an early stage of treatment research process, show benefits of Geodon in the treatment of psychosis. We found no studies on Seroquel.

The recent literature continues to bear out consistently the same adverse events associated with atypical psychotics [sic] that the working group found.

In closing, I respectfully ask that the advisory committee consider these points in tomorrow's votes: first, that over the three

years since APA released the finding of the working group, serious questions have not been answered regarding the long-term --

DR. GOODMAN: Thank you, Dr. Brown. Thank you.

Dr. --

DR. ZUCKERMAN: I'm Dr. Diana Zuckerman. I'm president of the National Research Center for Women and Families, and I have no conflicts of interest.

My doctorate is in clinical psychology. My post-doc is in psychiatric epidemiology from Yale Medical School, and I have experience working with patients with bipolar and schizophrenia. I was on the faculty at Yale and Vassar, did research at Harvard and worked in the U.S. Congress and U.S. Public Health Service.

Our center is dedicated to improving the health and safety of adults and children, and we do that by scrutinizing medical research. I'm also a fellow at the Center for Bioethics at the University of Pennsylvania.

The new FDA commissioner has said she will refocus the FDA on its public health mission, and this is the great place to start, and that's your task today and tomorrow. The key question is, do the benefits outweigh the risks for children taking the three drugs under consideration today? And that question must be answered in the context of the risks and benefits of other drugs that are already available.

Since all three drugs are available and, in fact, about a million prescriptions written for children ages 13 through 17 per year for these drugs, you also need to consider whether FDA approval would send an inappropriate message of safety that is not supported by the research.

There's a lot of pressure in this room to approve these products, but that should not influence you. Your task is to independently scrutinize the data, to consider the impact of approval and to decide with any of these three drugs are proven safe and proven effective for long-term use by adolescents compared to other

available products.

And remember that in exchange for doing these studies, the companies have received patent extensions worth many millions of dollars, so they've already benefitted from doing this research. You don't have to feel sorry for them or worry about hurting their feelings. But you do need to determine if they've done right by our children and our psychiatrists by proving that their drugs are safe and effective for long-term use for these long-term disorders.

Unfortunately, the studies are inadequate. The samples are too small. The double-blind studies are too short, and even the open-label studies are too short. And they provide really no useful information about the long-term risks of tardive dyskinesia, sudden death or diabetes.

But there's a growing research literature, as well as these studies themselves, that show how high these risks may be. And even the studies that have been presented today show

significant risk of weight gain, sedation and other serious side effects -- and that sedation could be showing improvement on the mania scale because the kids are sedated rather than truly less manic.

So the known risk are too great to approve any of these three drugs for bipolar disorder because there are other drugs that are safer, less expensive and equally or more effective, and there are some antipsychotics already available.

Now, some kids may need some of these drugs, but they will already be available off-label, as they are now. So they should not be approved, not even as a second-line drug because, if they are, they will be advertised and used much more widely as first-line drugs.

Do the benefits outweigh the risks for schizophrenia? It's impossible to say because the data -- again, too short, too few kids, and not long term enough to really tell us anything.

And if there's any time left, I would

love to answer any questions about the Russian placebo group, which I've looked at carefully, and is very --

DR. GOODMAN: Okay. Thank you very much.

MR. MACK: Good afternoon. My name is Steve Mack. I'm here to talk about Cymbalta discontinuation syndrome, what it's all about. I was prescribed Cymbalta for ADD. I took it for about seven months, and then I went off it, and I had a terrible discontinuation experience, so that's what brings me here today.

I apologize for the small font. I wasn't aware that this room would be so large. Hopefully most of you area aware of, you know, what discontinuation is all about. It can be really severe. Cymbalta is generating a huge inventory of people that have been traumatized by the discontinuation, and there's some of the symptoms up there that are common across the entire complex of people that take the drug, or have taken the drug.

These are the claims that I'm presenting

about Cymbalta. One, Cymbalta discontinuation syndrome is more severe and more widespread than acknowledged by Eli Lilly.

Two, that the sales reps and the marketing materials don't adequately convey or inform the physicians about the discontinuation syndrome.

Three, the direct-to-consumer advertising is misleading.

And, four, Lilly has not developed and fielded a clinically proven protocol for safety discontinuing, so once you get on, you can't get off.

This next slide -- it's basically a weak inference about the scope of the syndrome. These are the number of web captures from a search on Google using Cymbalta or a drug name, plus withdrawal. And the counts here for Cymbalta are almost a million and a half, Paxil a little over a half million, Effexor a little over a half million. And so -- and the release dates are Cymbalta 2002, Paxil 1992 and Effexor 1993. So

you have these huge counts of Cymbalta when it's released much later than these other drugs, and the question is, you know, why? Because these submissions on the web are spontaneous and independent, so it's got to tell you something.

These are just a listing of some of the websites -- there's now scores of websites that collect anecdotes about Cymbalta withdrawal. And -- and bullet number 4 I think is kind of interesting. It's called the point of no return. It's a third-party withdrawal assistance, and the question is, you know, why should somebody have to pay to get off Cymbalta?

The fifth bullet is just kind of interesting -- YouTube video that kind of documents what it's all about, withdrawing. And -- I mean, somebody took the effort to make that, so the question is, why?

These are some of the typical Cymbalta withdrawal anecdotes. I'll just quickly make some notes. Note the date, May 15th, 2009. So people are submitting these seven years after the drug

had been released. The date -- the person here notes that he's on day 38 of his withdrawal, which indicates that he's six weeks into a very difficult process. Serious life challenges, rage, confusion, dizziness. These are just common complaints that are suffused throughout these websites.

Bullet number 2. Lilly reps' marketing materials do not adequately inform physicians. Obviously the physician, if he doesn't know, he or she can't, you know, deal -- talk to their patient properly.

The practical effects are that the patient undergoes withdrawal, and then essentially becomes disengaged from the physician, so the doctor-patient relationship is wrecked. And that's just a process flaw that -- there's really no excuse for it.

I'm really behind now. The next couple of slides basically are just screen captures. You can read through those.

I'll just go to the end here, some of the

observations. And I only have 15 seconds -- I have 10 seconds. The only point I want to make that the next bomb to hit is fibromyalgia wave of Cymbalta discontinuation distress. That's inevitable because, you know, if psychs don't know, nobody else will.

DR. GOODMAN: Thank you, Mr. Mack.

MS. RESKO: Good afternoon. I'm Susan Resko. I'm the executive director of the Child and Adolescent Bipolar Foundation. I represent over 25,000 constituents. 95 percent of those are parents. CABF neither seeks nor accepts support from the pharmaceutical industry.

Despite the public dismay over recent research findings showing a 40-fold increase in the diagnosis of bipolar disorder in children, research over the past 15 years has repeatedly validated the existence of this illness in children. In fact, diagnostic rates in children are still well below those in adults.

Federally funded studies also reveal that child-onset bipolar disorder is more severe than

the adult form of the illness. Youth with untreated bipolar disorder are at increased risk for school failure, substance abuse, failed relationships, legal difficulties and even suicide.

Suicide remains the third leading cause of death among teens and young adults. 90 percent of youth suicide victims have a major psychiatric disorder, most often bipolar disorder or depression.

It is for these reasons that youth need early recognition and access to treatments. In many cases CABF parent report that these medications under consideration today are life-saving. Parents report that these medications allow a child to remain in the home, function at school and experience positive social relationships.

However, these medications can have serious side effects, which must be carefully weighted against the risks of not treating the illness. CABF urges you to take the following

into consideration.

First, more long-term studies are needed on the safety and efficacy of these medications in children and adolescents. Children are not little adults, and their bodies do not respond to medications in the same way. We know that children take these medications for years, and parents and clinicians need better information about long-term use.

Second, require appropriate monitoring recommendations so that parents and clinicians can carefully evaluate treatment effectiveness against possible side effects. Monitoring recommendations should be cost-efficient and based on research results; otherwise, they act as a barrier to treatment.

Third, if medication guidelines are developed, please include parents in that process so you will have an effective communication piece.

And, fourth, if you choose to approve these medications, limit direct-to-consumer advertising in favor of more long-term studies for

a time period. More research will provide better treatments with fewer side effects for our children.

Thank you for your time and consideration on behalf of America's children.

DR. GOODMAN: Thank you very much.

MS. EARLS: Good afternoon. I have no conflicts with the entities cited.

My name is Elizabeth Earls. I'm the president and CEO of the Rhode Island Council of Community Mental Health Organizations. I also serve as board chair of the National Council for Community Behavioral Healthcare. The national council is a national not-for-profit organization representing over 1600 community behavioral health organizations across our country, providing treatment and rehabilitation to children, adolescents and adults living with mental illnesses and addiction disorders.

National council members represent the public sector safety set for millions of individuals with severe and persistent mental

illnesses, and provide a whole range of recovery and person-centered treatment and support services.

Every day community mental health centers encounter families in crisis. Half of all lifetime cases of mental illness occur by age 14, three-quarters by age 24. When it comes to serious mental illnesses, such as bipolar disorder and schizophrenia, early recognition and treatment is critical to creating an opportunity for a child's future, to not be defined by a disability, but by hope, resiliency and recovery.

Experienced behavioral healthcare practitioners, working in a therapeutic partnership with families, develop comprehensive treatment plans that may include psychotherapy, social supports and, in many cases, medication.

Access to safe and effective medications is crucial to treating these serious and complex conditions in children and adolescents. Appropriate diagnosis and medication can mean the difference between a child remaining within his or

her family, succeeding in school and developing positive social skills and supports or not.

As healthcare providers, working in local communities across the country, we urge the Federal [sic] Drug Administration to carefully consider the importance of pharmacologic treatment options for bipolar disorder and schizophrenia in children and adolescents.

In addition, today's meeting provides us the opportunity to ensure that families who are experiencing the devastating impact of mental illnesses and their providers who support their recovery have the information needed to make meaningful decisions that include education about their illness, ongoing reviews of the effects of the prescribed medications, and information about the availability of community supports and a range of rehabilitation services.

Families must have all the information and support needed to decide upon the safest and most appropriate and effective treatment available for their condition.

The welfare and optimal development of children or adolescents is of utmost concern to everyone here. We encourage an open and transparent scientific discourse about all pharmacologic treatments that come before the advisory committee and urge the committee to carefully weigh available evidence regarding safety and efficacy. Thank you.

DR. GOODMAN: Thank you very much.

DR. CLARK: I'm Dr. Carl Clark, and I do not have any financial conflicts of interest with the sponsors. I'm here today as a psychiatrist and the CEO of the Mental Health Center of Denver. We're a not-for-profit community mental health organization.

I urge the FDA to continue to carefully weigh the available evidence regarding safety and efficacy. It's also critical that the FDA conduct the necessary monitoring and communication to mental health professionals and families to ensure the safe use of drug treatments with children and adolescents.

We know that any organ in the body can develop an illness, including the brain, and as a psychiatrist, I am partial to the brain. I think it's the most important organ in the body. No one likes to think about children getting ill, but children and adolescents can develop depression, bipolar disorder, schizophrenia and other conditions that affect their learning and development. Untreated, young lives can slip into hopelessness and despair and be lost forever. Children deserve access to treatment.

They also need appropriate treatment to grow up to be happy adults, to succeed in school and to become valuable members of our community.

When prescribed appropriately, psychotropic medications can be life-saving. Achieving the appropriate balance between clinical effective use and the known risks and side effects associated required individualized medical decision-making.

To provide the optimum treatment, mental health providers must have access to a range of

psychotropic medications. At the same time, we need to be extremely careful in using drugs as a first-line treatment without the needed psychotherapy services that can help the entire family.

My father had bipolar disorder, and when he was growing up, he was undiagnosed. He didn't get diagnosed until he was 36. After he got onto his treatment, after struggling with the idea of having a mental illness, he told me that he wished that people had noticed that he had this illness when he was kid. He wondered if the trajectory of his life's career would have been different had people noticed that he had the illness and had treatment been available.

When I told him I wanted to become a doctor, he asked me what the hell I wanted to do that for. When I told him I wanted to be a psychiatrist, he said, you're going to do something useful with your life.

So I'm telling you this because, on behalf of my father and people who suffer from

illnesses when they're children, having these medications available is very important. Thank you.

DR. GOODMAN: Thank you.

MS. HAVENGA: Good afternoon. I'm Shirley Havenga from Seattle, Washington. I'm the CEO of Community Psychiatric Clinic there. I have no conflict or interest with any of the entities cited.

At my clinic, Community Psychiatric Clinic, we have for the past 50, have helped thousands of individuals and families cope successfully with everything from the challenges and stresses of everyday life to serious mental illnesses.

As you consider important treatment options for bipolar and schizophrenia in children and adolescents, I encourage you to utilize all of the FDA's resources to, number one, monitor the performance of any approved psychotropic medications used to treat children and adolescents and, number two, to communicate this information

to prescribers, mental health professionals, families and patients, to help ensure the safe use of drug treatments.

It is essential that clinical oversight and guidance be provided to ensure that the utmost care is taken and that, for children and adolescents, drug treatment is used in conjunction with the comprehensive use of evidence-based psycho-social treatments.

We know that one in ten youth have mental health problems that are severe enough to impair how they function at home, school and in the community. A greater proportion of children and youth in the child welfare and juvenile justice systems have mental health problems than in the general population. In fact, about 70 percent of youth in the juvenile justice system have a diagnosable mental health -- mental illness disorder.

Just as alarming as that fact is that one in five of these children receive services from mental health professionals. The consequences of

untreated or improperly treated mental illnesses in children and adolescents are well-documented and include homelessness, incarceration, suicide, school failure, dropout and hospitalization.

A leading child psychiatrist once said that youngsters can only be understood by considering the complex, interlocking web of caregivers, family neighborhood and community that surrounds them, and that changes over time.

When we are examining the mental health treatments of children and adolescents, there must be a recognition that we are dealing with many factors influencing their psychological, cognitive and behavioral functioning. This complexity, therefore, requires a higher level of surveillance and communication by the FDA.

There is still so much for us to learn about what works, especially in the area of most severe mental health conditions. We also face challenges with appropriate prescribing and monitoring medications at home and at school, and the need for parents to be fully educated and be

prepared to evaluate the risks and benefits of pharmacological treatments.

There needs to be an active partnership between the prescriber and the children and youth receiving treatment and their families.

I thank you for the opportunity to speak with you today.

DR. GOODMAN: Thank you.

MS. ROSOLINO: Good afternoon. My name is Renee Rosolino, and I am here on behalf of Families for Depression Awareness. I have not been paid to be here today, but they did pay for my travel.

Ten years ago I was diagnosed with bipolar disorder. After living with a parent with depression, I was first in denial that I could even have this illness. I was angry. But most of all, I was afraid of what my family and friends would think and how my life was going to change.

At first, I refused all treatment and the idea of being on medications. Unfortunately, my behavior became very erratic, harmful to myself,

and the depression worsened. I didn't sleep. I was unable to cope. The daily activities -- I couldn't care for my family nor myself.

I finally agreed to seek treatment after intense pressure from my husband and my loved ones. I did meet with a psychiatrist. However, I did not want to take any medications. I saw what they did to my dad. But because I was not medicated properly, my symptoms continued to intensify, and I had to be hospitalized.

After several weeks of aggressive treatment, I was able to leave the hospital on an outpatient program. This was a circle for many years. When I was hospitalized for an overdose of medication years later, I was put back on meds after I had gone off of them, and I was taken -- my decision to choose what meds I wanted to be on was taken away from me. My doctor and my husband at this time decided what antipsychotic medication I needed to stabilize me at that time.

I was unable to communicate at this point, so my opinion in this matter was not

warranted. I was put on Zyprexa. However, I did not respond to that positively, so they decided to change to Seroquel. I did respond to it positively, and I began to improve.

After being stabilized for a few years, I decided I wanted to cut back on my medications and to stop the Seroquel. My doctor did not agree with this idea. However, I was adamant about it, and I said that's what I wanted to do.

After a year, I began to decline once again and had to be hospitalized. I was put back on Seroquel, and it took some time to regulate me. However, eventually, with the love and support of my family and my friends and a very dedicated doctor that would not give up on me, aggressive treatment and a very strong faith, I did stabilize once again.

I have not had to be hospitalized in the past four years, and I have been off all medications for the past year and a half. Today, again, I lead a very active and productive life. Being off all medications is against my doctor's

orders; however, I do accept the fact that one day I may need to put on these medications again.

I have an open agreement with my doctor, my husband, my children and other family members that at any time they can call her and speak with her if they see that my behavior becomes erratic or harmful again.

I'm here today to tell you my story because I am able to stand before you because of these medications and the love and support of my family and my doctor. But the negative stigma of these medications has to be dealt with. I know that without these medications it's very likely that I would not be standing before you today.

After having to take on many different combinations of medications to stabilize me, I know that not all medications work for everyone the same way. Everyone has a different chemical makeup and responds to medications differently. What works for one person may not necessarily work the same for the next, but isn't that true for many medications, regardless of the illness that

it treats?

Many medications have warning labels of possible suicides. These warning labels are not just on depression or antipsychotic medications.

For the past years, I've been a volunteer at the Families for Depression Awareness. Although it's difficult to tell my story at times, I feel that it's necessary. I run a support group, and I feel that it's my job to help encourage people to find the right doctor, the medication, supportive treatment, to learn coping skills so they can, once again, lead that healthy life.

I'm not a professional on these matters; however, I'm just a person diagnosed with bipolar disorder that has been blessed with being able to live with this disease effectively. I only speak of my personal experience today, knowing that -- thank you.

DR. GOODMAN: Thank you very much.

MS. PORTES-ANTOINE: Good afternoon. My name is Stephanie Portes-Antoine, and I have no

conflicts of interest. I'm here today to make a statement on behalf of the Patient and Consumer Coalition, which is a coalition of public health, consumer and scientific non-profit organizations and associations. We are very concerned that this advisory committee is being asked to vote on whether three antipsychotic drugs are acceptably safe for adolescents rather than safe.

While we understand that FDA approval is based on a risk-to-benefit ratio, the changing of the standard from safe to acceptably safe is not clearly defined and seems to lower the standard. This is not acceptable.

In addition, the double-blind studies being provided to the advisory committee are very short-term, just a few weeks in duration, which is not a long-enough period of time to make a meaningful determination of safety or efficacy for schizophrenia or bipolar disorder.

And, yet, the advisory committee is being asked to consider expanding approval for three drugs that are approved for adults despite

well-known and very serious long-term risks, to make them even more available for children.

We need to hold these drugs to higher standards. They should be proven safe and effective for long-term use, since the treatment will be long-term.

The coalition groups include the Community Access National Network, the National Research Center for Women and Families, Consumers' Union, D.C. Psychological Association, Government Accountability Project, Our Bodies, Ourselves, the TMJ Association and WoodyMatters. Thank you for your time.

DR. GOODMAN: Thank you very much.

MS. BAGNO: Hi. My name is Christina Bagno, and I have no conflict of interest being here.

I'm the parent of a bipolar child. Some people don't believe that bipolar disorder can exist in children. I have a child, though, whose mood swings and corresponding rages are of such proportion that it would be impossible to provoke

them. She is not ADHD. She is not brain-damaged, suffering from seizures or the victim of bad parenting. She is seven-and-a-half years old, and she has bipolar disorder.

My former husband and I adopted Daisy from an orphanage in Belarus when she was 18 months old. As the developmental pediatrician strapped a raging, thrashing Daisy onto a papoose in order to administer her vaccinations upon coming home, the doctor assured me she was just spirited, smart, feisty. Give it time, she said, and gave me the number for early intervention.

A year of special education, itinerant teachers, physical therapists, speech pathologists and occupational therapists later, Daisy still raged. She still giggled uncontrollably for hours. Every two hours her mood turned upside-down, sometimes a "no" provoking it; others, no clear antecedent. I would awaken at 2:00, 3:00 in the morning to find my daughter, with her light on, jumping up and down furiously in her crib, laughing hysterically.

By the time she had turned three, we had tried it all: Sticker charts, time-outs, play therapy, positive reinforcement, super-nanny this, behavior modification that.

Finally, when Daisy threw the marble reward jar across the room into a glass door, I knew that she needed help, psychiatric help. I came to a point where we realized that unless medication could help her, she would have to be placed in residential care in order to keep her and us safe from her primitive, destructive rages.

The first psychiatrist diagnosed her with ADHD and prescribed a stimulant. I couldn't fill it. The diagnosis just didn't fit.

I researched my way to the Child and Adolescent Bipolar Foundation website. A parent there advised me to read The Bipolar Child. I did, and I immediately saw my daughter.

We went to see the author. Daisy bounced from his couch to his chair, telling him she felt like Tigger, all jumpy. He smiled and watched her carefully. Alone in his office, he told me yes,

based on the forms filled out, evaluations shared, video provided and observations here, your daughter seems to have all of the classic symptoms of early-onset bipolar disorder.

Hoping to avoid medication, we started with fish oil, then melatonin. Both activated Daisy, making her more manic. Finally, Risperdal.

A day or two into our trial, we sat at the park. Daisy ate pretzels and talked to me about the birds on the tree in front of us. My best friend nudged me when Daisy got up to play: Do you realize that is the first time I have ever seen Daisy actually sit down, eat calmly, and be able not only to notice, but discuss the world her?

She was right. Something had shifted. The Risperdal was working, and I was seeing my daughter peeking through her illness for the first time.

Risperdal did not hold Daisy indefinitely. At four, lithium was added to successfully combat severe depression. Seroquel

helped with hallucinations. Hospitalizations and more hallucinations. Medications adjusted.

Today, Daisy attends a therapeutic day school and takes Seroquel and lithium. She just enjoyed her first sleepover. She laughs, smiles, sleeps and night, gives and receives hugs, takes her medication and understands that it helps her feel better.

She still struggles, but the struggles are manageable now. Antipsychotics saved my child. Without them, a little girl who spent her first 18 months of her life in an orphanage would now be spending her childhood in a residential treatment facility. Instead, she is home with the people who love her, enjoying her childhood.

DR. GOODMAN: Thank you very much.

MR. BOEHM: Good afternoon. My name is Vince Boehm, and I'm an unpaid volunteer. I have no conflicts. I edit a private e-mailed news list that brings news items to a group of mental health professionals and other interested parties. One of my readers, Dr. Stefan Kruszewski, is a

Harrisburg, Pennsylvania psychiatrist, and he wanted me to read this into the record.

Dr. Kruszewski says, the clinical trial reports posted by AstraZeneca on the Internet for data obtained for the use of Seroquel in major depression and generalized anxiety disorder -- Dr. Kruszewski has demonstrated the following key points.

Clinical trials established that efficacy is modest, if at all, for either condition. The safety features include a host of adverse events, highlighted by serious and significant weight gain and changes in metabolic parameters. The risk-reward ratio does not favor Seroquel for either major depression or generalized anxiety disorder.

The newly posted Amber study has completely -- was a completely failed clinical trial. AstraZeneca demonstrated no efficacy for Seroquel as mono therapy in adult patients with major depression and significant adverse events.

These newly published data from

AstraZeneca's Amber study reinforce the main conclusion of Dr. Kruszewski's earlier submitted report to this committee.

Extension of Seroquel labeling to include major depression disorder, a common condition, could result in exposure to hundreds of thousands, if not millions of patients to substantial medical risks with minimal or no clinical benefit to justify these risks.

A cost benefit analysis would not favor the use of Seroquel in either generalized anxiety disorder or major depression.

For the record, for you, Dr. Stefan Kruszewski is a graduate of Harvard Medical School with post-graduate training in internal medicine and psychiatry at Harvard, Rutgers, Robert Wood Johnson and Duke, and he's got multiple board certifications, and he's licensed actively in seven states.

In closing, I plead the panel to heed this testimony, and that of others, not to allow the extension of Seroquel labeling, or the other

substances involved, to children and adolescents. And thank you so much.

DR. GOODMAN: Thank you. My name is Allen Jones. By way of disclosure, I am the relator in an unsealed qui tam lawsuit in Texas against the makers of the drug Risperdal. I have also consulted on lawsuits involving other atypical antipsychotics.

My concern today is that there are potential conflicts of interest on the panel. In recent years, Dr. Granger and Dr. Robinson have reported financial relationships with makers of antipsychotics. Other members have made past disclosures of financial relationships with the makers of other psychiatric drugs.

During his career at Yale and the University of Florida, Dr. Goodman was the principal investigator in over 50 clinical trials funded by drug companies. 16 of these trials involved Eli Lilly and Pfizer. He was also a consultant to the makers of three antipsychotics.

These relationships ended when Mr. Goodman came to NIMH. However, next month he

begins his duties as the chair of psychiatry at Mount Sinai School of Medicine which reports currently administering 915 non-government grants, including many from drug companies.

I do not claim that these conflicts make it impossible for the panel to exercise independent judgment. But I do believe it means that we need to take an extra step, an extra filter needs to be inserted in your deliberations to filter against any possible residual influence based on past or future associations.

If this were a civil trial involving two people and $3,000, many of you would be excluded from the jury. As it is, we're talking about maybe millions of people and billions of dollars. Please apply that extra filter of deliberation to ensure that you are making your decision based on the facts that you know, based on the facts that were presented here today, but also what you bring to the table.

You were selected for this panel because

of your expertise. Bring all of that with you to the deliberations, and very carefully exercise your professional judgment in filtering the information given to you by the drug companies.

Today you were charged with answering two questions relative to each drug: Are these drugs -- have these drugs been proven to be effective? And, have these drugs been proven to be acceptably safe?

Those are straightforward questions. If any panel member attempts to subdivide these questions into a longer list of more ambiguous questions, I ask the other panel members to ponder why this is happening; I ask you to please apply your full intellect and professional skepticism to any apparent shift in the dialogue.

The drug companies can obscure the safety hazards of these drugs in children. Recent revelations concerning Zyprexa and Seroquel contained in documents released confirm the companies withheld negative data. You must consider the presentations given to you today may

also be tainted -- may also include such omissions.

I do not envy you your jobs. If you make a wrong decision, you could literally be sentencing children to death. I ask you two questions of my own: Can these drugs cure anyone? We all know that they cannot cure. They will not cure any child. Can these drugs harm anyone? We all know that a significant percentage of children taking these drugs will sicken and many will die. Please consider that in your deliberations. Please be guided accordingly and please reject the expanded use of these drugs in the juvenile population. Thank you.

DR. GOODMAN: Thank you.

DR. GREENHILL: Good afternoon. My name is Larry Greenhill. I'm president-elect of the American Academy of Child and Adolescent Psychiatry. In the way of disclosure, over the past 24 months, I have received research support or have worked as a consultant basis with Otsuka, Johnson & Johnson, Forest, Pfizer and NIMH. I

have practiced child psychiatry, have federally supported long-term adverse event studies to look for the association with those events and psychotropic drugs, and practice -- and been a member of ACAP for 30 years.

American Academy of Child and Adolescent Psychiatry is a professional medical association of 8,000 child and adolescent psychiatrists established in 1953. It is the leading national medical association dedicated to treating the estimated 7 to 12 American youth -- million youth -- 7 to 12 million American youth under age 18 who are affected by emotional, behavioral, developmental and psychiatric disorders.

Bipolar and schizophrenia disorders are severe conditions which first appear in childhood and adolescence. No one treatment works well for all children and adolescents with these disorders, so we support a wide array of treatment options being available.

Although a few clinical trials have suggested that these antipsychotic medications may

be effective in pediatric populations, the lack of systematically collected safety data when youth are exposed for very long periods that may affect their development indicates the need for more large-scale phase 4 studies.

We ask the FDA committee to carefully consider whether the number and scope of clinical trials, as well as the duration of the safety trials to date involving children and adolescents justifies the labeling changes being requested today.

While these medications may be helpful and even life-saving for some children and adolescents suffering with these disorders, there are significant metabolic and cardiological side effects for all youths exposed chronically to the medications, not just those that have the disorder, that need to be closely monitored.

For those reasons, we ask that the FDA use this opportunity, if they do approve any of the indications, to couple those indications with a requirement that these medications be registered

in a registry and particularly in large practice HMO settings where electronic health records and pharmacological prescription data can be aggregated and compared.

The resulting systematically collected information on the risks and benefits of these medications, as well as specific methods for monitoring for adverse events over time must be made available to physicians and families on a regular and timely basis, particularly before any approval of direct-to-consumer marketing be awarded to the sponsors about these medications. I think that's crucial.

Thank you very much for the opportunity for commenting on these questions.

DR. GOODMAN: Thank you.

DR. FASSLER: Good afternoon. My name is David Fassler. I have no conflicts to declare. I'm a child and adolescent psychiatrist practicing in Burlington, Vermont. I'm also a clinical professor of psychiatry at the University of Vermont. My testimony today is on behalf of the

American Psychiatric Association, where I serve as secretary-treasurer.

Since my time is brief, let me emphasize a few key points. First, schizophrenia and bipolar disorder are very real illnesses which collectively affect between 1 and 3 percent of all young people.

Second, these are also extremely serious conditions, with very significant consequences. Without treatment, children have problems at school, at home and with their friends. They're also at increased risk of accidents, hospitalization and death at an early age from multiple causes, including suicide.

Fortunately, treatment is available. Medication, including the atypical antipsychotics, can help reduce the symptoms associated with these disorders, but medication alone is rarely an adequate or sufficient intervention. It should only be used as part of a comprehensive treatment plan, individualized to the needs of the child and family.

As you've heard, the medications we're discussing today have very significant and well-documented potential side effects. There's also legitimate concern about the rapid increase in the use of these medications in children and adolescents. None of these medications should be used without careful consideration of the risks and benefits.

Nonetheless, when used appropriately, they can be a helpful and effective component of treatment for children and adolescents with schizophrenia or bipolar disorder.

Let me conclude with the following specific recommendations. First, I'd urge you to consider the reality of how medications are used in the treatment of children and adolescents with complex psychiatric disorders. In actual clinical practice, these medications are not used on a short-term basis. Many young people are treated for months, and often years.

In contrast, most clinical trials reviewed in conjunction with FDA approval are

relatively short-term, making it difficult to draw definitive conclusions regarding safety or efficacy over a more extended course of treatment.

Accordingly, it would be appropriate to limit any specific action or approval to short-term or episodic use, consistent with the data presented.

I would further urge you to encourage, if not require, pharmaceutical companies to conduct phase 4 studies which would address safety and efficacy when these medications are used on a long-term or ongoing basis.

Second, we need more studies which compare multiple medications with respect to safety and efficacy. Such head-to-head trials would help provide the kind of data physicians and family members need most in order to make fully informed decisions about treatment options.

And, third, I'd urge you to consider recommending a moratorium on direct-to-consumer advertising for a period of time following initial FDA approval of any specific indications currently

under consideration. Although personally I think such a policy is reasonable in general, such precautions may be particularly appropriate for medications such as the atypical antipsychotics where there's general agreement that we don't yet have sufficient data on long-term safety and efficacy in pediatric populations.

Thank you for the opportunity to share these thoughts, comments and recommendations.

DR. GOODMAN: Thank you.

MR. SPILLER: Good afternoon. My name is Lee Spiller. I'm with the Citizens' Commission on Human Rights of Texas. We're deeply concerned about the approval of these drugs for younger children. You know, the two things I didn't hear mentioned in the testimony this morning were remission and cure. So we're taking drugs that don't result in remission or cure, apparently, but do have serious side effects, known side effects, known risks in the adult population -- heart problems, association with diabetes, et cetera. And now we're going to foist them off on kids? I

just don't agree with that.

The other problem with it is that if you approve for a younger age -- we've already seen that there's been off-label use of these drugs in kids. If we approve them for a younger age, we think there's going to be more off-label use on even younger children.

We've seen problems with this in Texas Medicaid. When we requested data from 2003 to 2009 for Texas Medicaid, we saw some stuff that really startled us. In 2003, there were nine Texas Medicaid infants, less than a year old, that got Zyprexa, three that got Seroquel, seven that got Risperdal.

Now, luckily, that stat went down over time. It's not true for the other age groups.

2003, there were 58 three-year-olds on Seroquel. By 2007, there were 89.

2003, there were 339 three-year-olds on Risperdal. By 2007, there were 669.

These are serious drugs with serious risks -- and some of the review information that

you all put together showed that the risk appeared to be stronger for the younger kids. This is a dangerous move. It's not a matter of doing post-marketing research. The truth is plenty of children have gotten these drugs off-label. We need to look at the epidemiological data now. We need to see if we're hurting children now. We don't need to be talking about approving these drugs without looking at that data.

And that's about all I have to say. Thanks.

DR. GOODMAN: Thank you.

MS. SHERARD: I'm Polly Sherard, and I bring with me no conflicts of interest. I'm a former executive board member of the Depression and Bipolar Support Alliance. DBSA is the leading patient-directed national organization focusing on the most prevalent mental illnesses. It provides up-to-date scientifically-based tools and information written so that regular folks, like me, can understand.

My thanks to Dr. Allen Daniels, DBSA's

executive vice president and director of scientific affairs, for providing facts and figures to support my remarks today.

Mood disorders and the impact they have on families are important issues globally. For me, it's very personal. My history has two very different stories. One is my father's, the story of a life half lived and ended early because he found no effective treatment for his illness.

The other is my story of a life fulfilled because, unlike my father, I had access to both effective therapy and, eventually, the right medication.

In the 1950s and early '60s there were virtually no drugs available to treat my dad's symptoms. When he was well, he ran a business, played championship golf and made enough extra money on the weekends playing gin to send me through college. During the decades that my father suffered profound depression, he was unable to work or even to drive a car.

My father died too young from a heart

attack, caused in no small measure, we believe, by his mood disorder.

Years later, in the '70s and '80s, when I was diagnosed with depression, my story had a very different ending. The combination of effective talk therapy and the right drug virtually eliminated my symptoms and gave me back my courage, my career, my life.

Both my children inherited a vulnerability for a mood disorder. They, too, were successfully treated with medication and talk therapy. Today, my eldest daughter is a licensed clinical social worker, specializing in the mental health assessment of very young children.

My family is living proof that early intervention can be a passport to a productive life. And my young adult children are critically important proof.

According to recent studies, up to 20 percent of young people suffer a mental, emotional or behavioral disorder. For adults with lifetime cases of mental illness, half showed symptoms by

age 14, three-fourths by age 24.

Given the severity of mental illnesses like bipolar disorder and its extraordinarily high risk for suicide, it's essential for us to look for better ways to treat these diseases in the early stages, or to prevent them before they begin.

In closing, I urge you to mobilize resources and put a careful coordinated process in place to find safer, more effective medications. I encourage you to move forward towards this goal so that all who suffer may benefit from the remarkable advances made since my father's untimely death nearly 50 years ago.

Thank you.

DR. GOODMAN: Thank you.

DR. SHERN: Good afternoon. I'm David Shern. I'm president and chief executive officer of Mental Health America, and Mental Health America does receive unrestricted educational grants from all of the pharmaceutical companies represented here today.

We are a hundred-year-old organization. This year, Mental Health America celebrates our centennial. We were founded in 1909 by a person who had bipolar disorder, Clifford Beers, who experienced horrific treatment in the Connecticut hospital system, both the public and private side and, after leaving the hospital, wrote a book called A Mind That Found Itself, about his path to recovery and the experiences that he had in those hospitals.

And our organization, from Beers' founding, with Adolph Meyer and William James, has really been dedicated to trying to improve the treatment of persons with mental illness and also to use effective prevention technologies to drive down the rates at which people become ill.

During this year, we've had an opportunity to reflect back on what has happened over the last hundred years, and we have, as everyone in this room knows, made enormous progress in terms of our ability to reliably diagnose, effectively treat and effectively

prevent persons from becoming mentally ill.

But I think as everyone in this room also appreciates, we've got a lot to do. Many of the concerns that have been raised today have to do with things that we need as a community to improve -- you know, diagnosis -- DSM-V is currently being developed, and we continue to try to refine and understand the dimensions underlying specific diagnoses.

We are coming to appreciate more acutely every day the heterogeneity of response in clinical populations and the limitations of trial data for answering all of the important questions that need to be answered about safety and effectiveness.

We have increasing evidence that early identification and treatment of persons developing psychotic disorder might reduce the conversion to frank psychosis by a substantial amount, and as I think you know, the NIMH is currently in the process of mounting an initiative to take a very systematic look at early intervention.

We know a lot. We've made a lot of progress in the last hundred years. But we've got a lot of work to do.

My recommendations to you with regard to the matter at hand is to weigh very carefully the importance of having a full range of treatment options for individuals to choose among, but that they be properly supported, that clinicians and patients be properly supported and fully understanding the potential risks and benefits of the decision that they make. And as several people have said today, to the degree to which you can mandate post-marketing data, systematically collected and rigorously analyzed to help us understand what happens when these drugs are used in larger-term settings.

We've come a long way over the last hundred years. We've got a long way to go to improve services to individuals and to guarantee access to everyone at an appropriate time that can be most beneficial to them in terms of their long-term recovery and full participation in the

community. Thank you.

DR. GOODMAN: Thank you.

MS. ORTIZ: Good afternoon. My name is Liza Ortiz, and I have no conflict of interest, and I'm from Austin, Texas. I'm here today to tell you about my family and our experience with Seroquel.

On January 19th of 2009, my son, Philip Christian Ortiz, died at the Dell Children's Hospital in Austin, Texas. My son was only 13 years old. His cause of death was acute Seroquel toxicity.

He was a very beautiful, talented, funny, outgoing, caring child, and there was never a day that passed that he never told me that he loved me.

Philip was a pleasure to raise, and he did all the normal things that healthy children would do. He went to school. He explored. Everything was normal.

When Philip turned 11, his childhood remained the same, except he began to start having -- hearing voices and thinking bad things

were going to happen to him and our family.

In 2008, after Philip was diagnosed with schizophrenia, Philip was put on a cocktail of medications. None of these medications helped Philip in his increasingly frightening world. Little did I know that Philip had less than a year left of his precious life left.

The cocktail of antipsychotic drugs that Philip was given was garnished with Seroquel and ended his life four days later.

Since Philip's death, I have learned about Seroquel. I wish I had known then the deadly risk of Seroquel. Nobody told me that it could ever hurt my son. I would have laid down my life gladly if I thought for one minute Philip could breathe again.

As I was in ICU and I saw Philip's body so stiff and rigid with seizures that his hands twisted in ways that I never though possible -- as Philip's dad, his grandmother and I are all in the room, we start to see the bed shaking and Philip

started having seizure after seizure without end.

It seemed like the whole nursing staff at the ICU was in the room doing chest compressions to get a pulse. In a matter of minutes, with no success, the doctor told Philip's father that they tried everything they could, but there was nothing more they could do. Philip was pronounced dead.

Seroquel was the cause of Philip's death, and the question lies with this committee whether they want to be responsible for another death of a 13-year-old child who is on Seroquel.

In conversation that I had with Philip way before his death, he stated to me, Mom, I want to save a life some day and help someone.

Philip isn't alive today to help someone, but I am Philip's voice today in hopes of saving another child's life that may be taking Seroquel and sparing another family from going through what myself and my family and still experiencing.

Thank you.

DR. GOODMAN: Thank you.

MS. KITCHENS: My name is Mary Kitchesn,

and I'm from Bandera, Texas. I have no conflicts of interest, and this is really a hard act for me to follow.

I'm so -- it's tragic. I'm going to tell you about my little boy Evan. I have four children, and my second born, his name is Evan -- wonderful little boy, but early on he was diagnosed with autism.

Not knowing what that meant, I went to doctors, much like yourselves, asking questions, seeking answers, wanting treatment. I wanted to fix it. I just wanted to fix -- ear infections, they gave him antibiotics that fixed it. They gave Evan drugs that did what they -- they would suppress one thing, and another problem would pop up. Nothing fixed autism.

In 2004, his behaviors reached a point that I couldn't take care of Evan at home. So I exhausted my family's resources, my children's college funds in excess of $40,000, and I placed my son in a residential treatment care setting.

When the resources were gone and I went

to go get my son, he hadn't improved. On all the drugs -- nothing helped him. I was greeted by Child Protective Services. They then took custody of my son and said that he posed a danger to my family.

After a grueling nine months, my son is home, but in the interim of that, there were side effects.

Immediately after my son was placed in there, within a week, his eyes were crossed, permanently crossed. We have amblyopia. Side effects that were visible ones were a decrease in communication, his comprehension, he had neutropenia on record -- for five months his blood levels never -- his white blood cell count was never above -- not one time -- 2.3. Continuing over seven months to go from 200 milligrams to 800 milligrams daily of Seroquel.

Hypothyroidism. He gained 56 pounds over seven months. All of it documented and well-recorded.

He had nightmares, and he thought that

there were bats on him. When I would hug him, I felt slight tremors in his deep muscles that turned into, over the course of months, visible trembling that you could see from across the room. I hate describing it.

I don't know the numbers you need to support my claims, but I did go back to the hotel and I did some calculating on what 7 beats in a minute does to a child over a year's time. 7 beats per minute in heart increasing is 420 an hour increase, 10,080 a day, 70,560 per week, and in one year's time a child's heart beats more -- according to AstraZeneca, 3,669,12 -- I can't even say it. It's pathetic. 7 beats per minute, and it's no significant finding?

I was recently cleaning out my closet -- and I had forgotten that I was introduced to Seroquel early. In 2003, before Evan was placed, I took Evan to a doctor, and he gave me a bunch of samples. It was an adolescent -- pediatric and adolescent psychiatrist. Sample pills, right here.

AstraZeneca is asking you to do -- they're asking for your seal of approval on a practice that they have been engaged in -- I know of -- since 2003.

I'm sick about it. I want to go back to Texas. I want to go home to my babies, but I thank you for these four coveted minutes with you.

DR. GOODMAN: Thank you.

MS. RING: Good afternoon. My name is Glenda Ring, and I have no financial relationship or conflict of interest with any of the parties presenting today.

I am speaking today in qualified support of the proposed new drug applications with -- recognizing the need for clearly defined, extensive, continued monitoring of safety and efficacy and sharing of this information with all prescribing practitioners and families and the public that will be using these drugs.

I am a retired registered nurse. I've worked in inpatient psychiatry settings, including an adolescent inpatient unit. My comments do not

represent my profession, but my personal advocacy for children and adolescents.

My support of the application is anecdotal and primarily based on observations of young people diagnosed with these disorders, although my comments are focused on schizophrenia.

Schizophrenia is a life-altering illness which, when left untreated, leads to difficulty performing activities of daily life, including attending school, having social relationships and caring for one's self.

The disorganized thoughts and altered perceptions of reality typical of schizophrenia can have a devastating impact on every aspect of life.

For this reason, I do support the new drug applications with the qualifications I mentioned before. I do not minimize the risk associated with these drugs or any medication. If there is a drug without possible side effects, I do not know what it is.

Recognizing the risk involved with these

medications, I feel strongly that diagnosing and treating and continued monitoring of psychiatric disorders in children and adolescents must be done by mental health professionals with extensive experience with children and adolescents.

Other causes of their symptoms, such as substance abuse, should be ruled out. I also think that prescribing decisions must include parent and patient education, with close monitoring, as I've said before, of efficacy and for side effects, and must also include psycho-social interventions.

Individual responses to medications vary, and side effects vary not only in individual people, but in the same person at different times.

I'd like to conclude by adding that we do not withhold treatment for kidney disease, anti-rejection drugs for transplant recipients, anti-convulsants for seizures, antibiotics for infections, or chemotherapy for cancer, all of which can have serious life-threatening side effects, because the benefits outweigh the risk.

I ask that the same consideration should be given in treating psychiatric disorders. Thank you for your time.

DR. GOODMAN: Thank you.

Diem has a request.

DR. NGO: We have one OPH speaker who has not checked in. If you're in the room, please speak up.

Okay.

DR. GOODMAN: In that case, the open public hearing portion of this meeting has now concluded. And we will no longer take comments from the audience.

Tomorrow, the committee will turn its attention to address the task at hand: The careful consideration of the data before the committee as well as the public comments. This will culminate in a vote on ten questions.

Let me remind the panel members once again not to discuss these issues with anyone until we reconvene tomorrow at 8:00 a.m.

I will see you then, and the meeting is

now officially adjourned.

(Whereupon, the proceedings at 4:45 p.m. were adjourned.)